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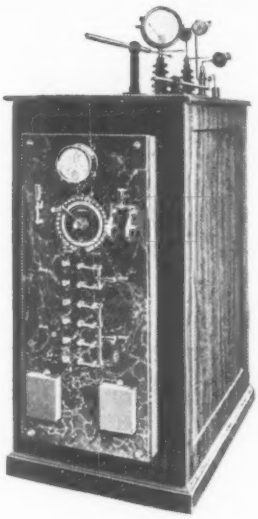

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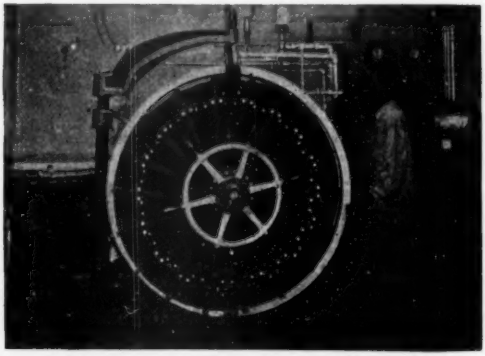

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The work with diabetes at the Hospital of the Rockefeller Institute began with feeding experiments on partially depancreatized dogs, and since then has grown in various directions. The results have been applied in the treatment of human cases, and this side of the investigation has been taken up by Drs. Stillman and Fitz, Dr. Stillman having studied especially the carbon dioxide changes in alveolar air and blood and Dr. Fitz the acetone bodies in blood and urine. It was a great good fortune when Dr. DuBois consented to determine the respiratory metabolism of certain patients at the Russell Sage Institute, and thus (in connection with the similar findings of Benedict and Joslin) some facts were established which were important for the intelligent application of the clinical treatment, and some theoretical questions decided and some others opened up. On the side of the animal experiments, Dr. Palmer has carried out a research in the practically unknown field of the sugar-content of the tissues under normal and various pathological conditions. Dr. Perlzweig and Miss Wishart are assisting in several problems, comprised chiefly under the topic to be discussed. The combination of animal and clinical work is very advantageous, each throwing light on the other. Also, the animal experiments are different from the customary, in that they do not consist in brief observations limited to a single point, but, on the

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contrary, animals are brought into the desired diabetic or other condition, and then are studied like human patients, through months and years if necessary. This plan has always appeared to me as indispensable for real progress in certain aspects of this problem. Acute experiments cannot give the best picture of chronic disease. Chronic conditions in animals need to be studied by the same combination of clinical, chemical, and microscopic methods as used for human patients, and for the same reason, namely, that one part of the picture can be understood only in relation with the other parts. On this plan, information is gained by determining the means to produce in animals the conditions occurring spontaneously in patients, and then by studying these conditions with the freedom and accuracy which are possible in animal experiments.

The problems of diabetic and normal metabolism are being opened up with surprising rapidity as methods become available. The monograph concerning my research at Harvard was written in 1912, and at that time comparative analyses at frequent intervals as shown in these charts were impossible, because the methods then existing required too much time or material. The present work was done entirely with methods published by American chemists within these few years. The numerous blood-sugar analyses were made possible by the method of Lewis and Benedict, which was used unmodified as originally described. The analyses for acetone bodies were carried out first with a modification of the methods of Shaffer, Marriott, and Folin and Denis, and later by the recent Van Slyke method. The alkaline reserve of the plasma was estimated by Van Slyke's simple and accurate device of the carbon dioxide combining power, which has proved its usefulness both experimentally and clinically. The blood-fat was determined by Bloor's method in the modification employed by Murlin and Riche. The methods introduced by Sellards and by Levy, Rowntree and Marriott deserve mention in connection with the study of acidosis, but had to be omitted in this research. It is evident that various blood and urine examinations, calorimetric studies, tissue analyses, and histologic and other investigations are most instructive when performed not upon different animals but upon the very animals for which these other data exist.

It has been decided to discuss the role of fat in diabetes because of its theoretical and practical importance, and because it has constituted one of the most confused and perplexed phases of the subject, where any light from any source may be deemed desirable. The feeding experiments mentioned at the outset have included the feeding of fat, and this has involved the longest and most difficult experiments of the series. Therefore, this opportunity is taken to present the results of some of the experiments in this direction, and this paper will consist largely of observations not heretofore published.

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It was formerly impossible to make a satisfactory study of this question with animal experiments because only two types of diabetic animals were known, namely, the Minkowski type, with total extirpation of the pancreas, and the Sandmeyer type, with removal of most of the pancreas and isolation of the remainder from its duct communications, so that the blocking of secretion brought on sclerosis and atrophy. Neither of these types of animals is capable of digesting and absorbing enough fat for the purpose, or of affording in other respects a sufficiently close reproduction of human diabetes, where there is ordinarily no deficiency of pancreatic digestion. I have previously described a method which gives a good approximation of the clinical condition. Those familiar with the publication will recall that this consists in removing most of the pancreas, leaving a remnant ordinarily of one-eighth to one-twelfth always communicating with a duct. With the smaller remnants the diabetes is severe; with the larger remnants it is mild; but by feeding the animals beyond their tolerance, so as to maintain a prolonged glycosuria, there is progress downward, as in human cases, and the mild diabetes becomes as severe as that which follows the more extensive removal of pancreatic tissue. For our present purpose and for most purposes the best results are obtained by having the pancreas remnants as large as possible, for two reasons. One is the avoidance of cachexia. The totally depancreatized dog dies within a relatively brief period, while an equal loss of sugar and nitrogen caused by phloridzin is far better borne. Some dogs with very small pancreas remnants do fairly well, but a large proportion of them fail to thrive, gradually emaciate, and die; whereas dogs with larger remnants but equally severe diabetes thrive much better. Nothing is known concerning the nature of this peculiar pancreatic cachexia; presumably it represents metabolic failure. The second reason referred to consists in the power of digestion. The digestion of the partially depancreatized dogs is never quite equal to the normal. Some of the diets used tax the digestion of normal dogs. In particular, the larger the pancreas remnant the better do the dogs dispose of a high fat diet. Occasional dogs become diabetic with exceptionally large pancreas remnants, and such animals are valuable for this use. In general, the program is to chooose young dogs as strong and as voracious as possible. The pancreatic tissue removed is the minimum required to produce mild diabetes. The tolerance is then broken down by overfeeding, the diet sometimes including several hundred grams of glucose daily until the desired degree of diabetes results. The animals are then often kept free from glycosuria for several weeks or months, and any tendency to recovery of too high a tolerance is checked by a period of overfeeding. In the best cases there is thus a decided hypertrophy of the acinar tissue, so that the remnant may come to equal as much as one-

fourth of the original weight of the pancreas, and yet the diabetic condition is maintained. Such dogs have highly satisfactory vitality and digestive power, and are very well suited for the fat feeding and other experiments. Though the internal secretory function has thus been injured largely by functional means, it remains fairly constant at its low level, and any recovery of tolerance is exceedingly slow. In this respect the animals resemble human patients. There is a difference in that the functional overstrain in dogs results in actual anatomical desctruction of cells in the islands of Langerhans, while such an anatomical effect in human patients is still doubtful.

The role of fat in diabetes will be discussed in its relation to three subjects.

I. Lipemia.

The first of these is lipemia. Here we deal with the disposal of fat from its absorption by the bowel to its taking up by the cells of the body. A few words may be devoted to the normal process, which is still obscure in essential points. An early dispute concerning digestion has been settled, since it is established that fat is not absorbed in emulsion as such but only as the split products. In the intestinal epithelium the glycerin and fatty acids are recombined into neutral fat. Some earlier researches, especially those of Rosenfeld and others in the dispute over fatty degeneration and infiltration, led to the view that this recombined fat is identical with the food-fat; that is, that only the fat synthesized from carbohydrate or other foods can be peculiar to the species, while otherwise the fat of the body takes its character from the fat of the food. A series of authors, Bloor being the latest, have modified this extreme view, and have shown that the epithelium changes and rearranges the constituents to considerable extent, so that the recombined fat differs from the food-fat in being more nearly like the natural fat of the animal. The procedure of splitting and recombination therefore apparently serves for the absorption of useful fats, the exclusion of non-saponifiable substances such as mineral oils, and the partial modification of the absorbed fat to resemble the specific body-fat. Some of this recombined fat is perhaps taken up in the blood capillaries and carried in the portal circulation to the liver. But at least 60 per cent. of it is known to enter the lacteals and pass in fine emulsion through the thoracic duct into the systemic circulation. Obviously, it cannot linger long in the blood, which would be hopelessly overloaded by the fat of a single meal. The cells remove it rapidly, so that, notwithstanding the heaviest intake, the blood-fat like the blood-sugar varies only within narrow limits. In the phraseology of Magnus-Levy, the level of the blood-fat must represent the balance between inflow and outflow at any given time.

This brings us to the consideration of the fat content of normal blood.

There have been described three physical forms in which fat may exist in the blood. First may be mentioned the occult form, which ordinarily predominates. The fine emulsion of the chyle is changed as it enters the blood stream. The droplets apparently dissolve, so that the clear blood plasma contains fat which cannot be colored by osmic acid or any fat stains or extracted by ether or other solvents, and can only be demonstrated by digesting the proteins with enzymes, acid, or alkali, or precipitating them with reagents such as alcohol. This fat is probably non-dialyzable and seems to exist in some colloid combination. The second form consists of surplus or less soluble fat, in microscopic droplets, the blood-dust or hemoconia. These can be stained with fat stains and extracted with fat solvents, and as they increase they make the plasma first turbid and then milky, as in digestion lipemia. The third possible form of fat is perhaps never normal. It is the form described by several authors when the plasma is cloudy or even opaque, yet cannot be cleared by the centrifuge; tiny droplets may or may not be visible under the microscope, but the substance is not colored by fat stains or dissolved in ether or chloroform. Boggs and Morris reported over 4 per cent. of this form of fat in the blood in anemic lipemia of rabbits. Bloor found that this form arises *in vitro* when certain abnormal (viz., diabetic or anemic) bloods are allowed to stand, the previously clear plasma becoming turbid. The three physical forms are presumably due to varying proportions and combinations of fats and lipoids among themselves, and possibly with proteins, salts, or other substances. Normal fasting plasma is clear and, according to Bloor, contains approximately 0.29 to 0.42 per cent. fat in human beings, and somewhat more, viz., 0.51 to 0.66 per cent. in dogs. Turbidity may appear within about an hour after a fat meal; it reaches its maximum in about six hours, and after twelve hours the plasma is again clear. The susceptibility to alimentary lipemia, in other words the balance between the digestive function and the assimilative function, differs in different species. Nothing is known concerning differences in the rate at which their tissues can take up fat. Rabbits are resistant to alimentary lipemia, and increasing the dose of fat merely causes diarrhea (Neisser and Bräuning). Sakai proved that rabbit blood has no unusual capacity for carrying concealed fat. Therefore it is possible to accept the explanation of Kreidl and Neumann, based on dark-field examinations of hemoconia, that intestinal absorption of fat is much slower in herbivora than in carnivora; but the question has not been investigated chemically, and offers a promising opportunity for the use of the new micromethods. The goose has such a digestive power that it can be enormously fattened by forcible feeding; and in the serum of such stuffed

geese Bleibtreu, also Hervson and Sedel, found some 6 per cent. fat, though the rye used in Bleibtreu's feeding contained only 1.5 to 2.5 per cent. fat. Stuffing geese with fat-free food did not cause lipemia. Man and the dog are intermediate between these extremes. Alimentary lipemia between 1 and 2 per cent. is probably the highest that ever occurs in normal human subjects. Munk and Friedenthal found as high as 3 per cent. alimentary lipemia in dogs. It is impossible to produce in dogs a lipemia equal to that of the stuffed goose by any quantity or duration of fat feeding, for the digestion breaks down before any such plethora is produced in the metabolism.

Thus far the word fat has been used in the old-fashioned sense, indicating the whole of the ether-soluble constituents. But aside from the neutral fat, which preponderates, and the soaps and free fatty acids possibly occurring in small quantities, there are constantly present the substances called lipoids, grouped under the titles lecithin and cholesterol. Such phosphatids and sterols exist in every living cell; they are evidently of the most indispensable importance somehow, but their function is practically unknown. Even the gross metabolism of lecithin and cholesterol is mostly unknown. They can be absorbed as such from the bowel and also synthesized by the body. Cholesterol especially is excreted through the bile and feces. The nervous system is rich in these substances, and the liver, the red corpuscles, and the adrenal cortex have all been claimed to play a part in their metabolism. Bloor finds that the lecithin and cholesterol are each about a third of the total ether-soluble extract of normal blood. Their ratio is fairly constant and remains so in most pathological conditions, suggesting an important relationship. The quantity of glycerides in the fasting plasma might possibly be zero, which would mean that the entire transport of fat would be in the form of lecithin and cholesterol esters; but a small quantity of simple fat is probably present. Digestion of fat brings an increase in the glycerides.

Both lecithin and cholesterol rise in most forms of lipemia. Lecithin is markedly increased in alimentary lipemia even though the ingested fat be practically free from lecithin. Terroine, Hagenau and others observed a similar parallelism between fat and cholesterol even when the food fat was extremely poor in cholesterol; and Sakai laid down the rule that there is no lipemia without cholesteremia, supposedly because of the solubility of cholesterol in fat; and Gardner and Lander have pointed to an absorption of cholesterol from the bile; but Bloor has found no change in the cholesterol during alimentary lipemia. The occurrence of the lipoids free or in esters or other compounds may have special significance, but this is unknown at present.

The relations in plasma and corpuscles also deserve notice. Normally, according to Bloor, lecithin and cholesterol are nearly

equal in the plasma; the lecithin content of the corpuscles is approximately double that of the plasma, and also double the cholesterol of the corpuscles. Bloor assumes that two-thirds of the plasma cholesterol is combined in esters. It is believed that all the cholesterol of the corpuscles is free. The corpuscles contain no true fat or only indeterminable traces.

Connstein claimed that the presence of red corpuscles is necessary in order for the fat to be changed from the emulsified to the soluble form. Munk and Friedenthal asserted that the corpuscles actively take up fat, so that in alimentary lipemia they may contain a higher percentage than the plasma. Bloor has confirmed this statement, and furthermore has found that lecithin increases chiefly in the corpuscles and only slightly in the plasma. Following up the idea of Loew and of Leathes that all fat is utilized *via* lecithin, Bloor has set up the hypothesis that all or most of the absorbed fat must be taken into the corpuscles and converted into lecithin before it can be assimilated. He finds here an explanation of the arrangement whereby fat is led into the general venous circulation to be thoroughly mixed with the blood before being carried to the liver or any other capillary domain for assimilation. Since lecithin is increased in a brief lipemia, as during digestion, he assigns special importance to it in the early stages of assimilation; and as cholesterol is increased in lipemias of long standing, he ascribes importance to it in the later stages of assimilation of fat.

The actual mechanism by which cells take up fat is unknown. Authors from Hanriot to Rona and Michaelis, Caro and Sakai have undertaken to demonstrate a lipase function. The process in assimilation would thus correspond to that in digestion. But the alleged lipase is so feeble that its presence or activity is hard to determine accurately by titration, and recourse is had to delicate physicochemical tests with the stalagmometer. Also, it seems truly characteristic of the subject of diabetes that the attempt should be made to explain lipemia by diminution of lipase, disregarding the extreme diminution of lipase in diseases without lipemia, as reported, for example, by Bauer. The lipolytic enzyme of blood seems classifiable with the glycolytic enzyme as accidental and unimportant, and the notion of enzymatic digestion of fat in the blood plasma or at the cell boundary does not merit serious consideration. On the other hand the conversion of fat into the plasma-soluble form, through the process supposed by Bloor or any other process, appears as a significant phenomenon. All living cells contain a similar "masked" or combined fat, and the most plausible view is that fat passes through the cell boundaries in this colloid or soluble form. Taylor refers to this as the "metabolic" form of fat. Nevertheless, it must be borne in mind that we are dealing with hypotheses throughout, and that nothing

is known positively concerning the means by which the cells take up fat from the blood.

Except after meals it seems probable that hyperlipemia is abnormal like hyperglycemia. A slight lipemia accompanying exercise was observed by Murlin and Riche. Bloor suspects that excitement may increase blood-fat as it does blood-sugar. Animals possessing stores of fat show a slight lipemia during fasting, supposedly because of increased transport of fat. Bloor's highest figure was about 0.9 per cent. Slight lipemia may occur in pregnancy, but according to studies by Klinkert and others, cholesteremia is the most prominent feature, and is responsible for the occasional xanthelasma and possibly related to the accompanying hypertrophy of the adrenal cortex. Just as hyperglycemia, so also hyperlipemia may occur in various metabolic disorders. It may be found in obesity, alcoholism, and nephritis. Chauffard and Grigaut described hypercholesteremia in nephritis. According to Lauber and Adamuck, Zinsberg and Chauffard the white flecks in the retina in nephritis are largely accumulations of cholesterol esters, and (Borberg, Landau) cholesterol is increased in the adrenal cortex. The familiar accompaniments of nephritis, namely, atheroma of bloodvessels and the arcus senilis of the cornea, likewise represent deposits of cholesterol esters. J. Müller reported an unusual case of nephritis, with chylous hydrothorax, and the above-mentioned opacity of the plasma which cannot be cleared by the centrifuge or fat solvents or stained with fat stains. Here the blood contained over 3 per cent. total fat, and 0.6 to 0.8 per cent. each of lecithin and cholesterol. Cholesteremia and lipemia are present with icterus, gall-stones, and liver disease, as shown by Klinkert and Beumer and Bürger. Cholesterol is deposited in the xanthoma formations and the cholesterol content of the bile is said to be increased. Lipemia has also been reported in pneumonia, heart disease, dyspnea, syphilis, and esophageal cancer, some of these cases being perhaps mere alimentary or inanition lipemia. The lipemia in a number of other conditions named by Fischer is doubtful. Experimentally, slight lipemia occurs in poisoning with phosphorus, phloridzin, and other drugs causing fatty degeneration, and during and after narcosis, though the phenomenon is inconstant (Murlin and Riche, Bloor, Lattes and others). Fat emulsions injected intravenously are rather promptly disposed of by the liver and other tissues, and lipemia is resisted. Bloor's highest figure after such injections is 1.5 per cent. blood-fat. It is well known that intoxication with fatty acids has been suspected in the etiology of some clinical anemias. The analyses of Freund and Obermayer, Erben, and Beumer and Bürger show lipemia absent in pernicious anemia and some cases of leukemia, and in other cases of leukemia a slight lipemia up to 0.7 per cent. Bloor gives similar findings in pernicious anemia, with the sugges-

tion that the low cholesterol values may be significant in view of the protective action of cholesterol against hemolytic agents. Boggs and Morris observed lipemia in a man with anemia secondary to hemorrhoids. They compared it with lipemia which they discovered in rabbits made anemic by repeated bleedings; they found no lipemia in cases of equal anemia produced by pyrodin poisoning. In the anemia of phenylhydrazin poisoning, Sakai described lipemia of approximately 1 to 3 per cent.; and as observed by Underhill, fatty liver and hypoglycemia accompany such poisoning. When the anemia was produced by bleeding, Sakai found values almost up to 6 per cent. blood-fat, with proportional increase of lecithin and cholesterol. These are the highest figures ever reported for non-diabetic lipemia.

We come now to the principal metabolic experiment which nature has performed for us, namely, diabetes. Just as there is no other way of producing hyperglycemia equal in intensity and duration to that of diabetes, so also the lipemia present in some cases of diabetes is beyond parallel in any other clinical or experimental condition. In blood taken from a thirteen-year-old diabetic child three days before death in coma, Frugoni and Marchetti reported a total ether extract of 27 per cent., and in blood from the same patient at autopsy 34 per cent. The highest figures fully accepted by German authors are 19.7 per cent. by Neisser and Derlin and 18.13 per cent. by B. Fischer. For comparison it is interesting to note that the highest known value for fat in thoracic duct chyle by Zawilsky, with maximal fat feeding in dogs, was only 14.6 per cent. Sakai reckoned that the blood in Fischer's case contained over 700 grams of fat. There are numerous reports of all grades of lipemia below this. Imrie has described one of the most recent cases, with over 14 per cent. fat in the blood. The most comprehensive chemical study has been made by Bloor, who gives complete analyses in thirty-six of Joslin's patients. He found the blood-fat normal or even subnormal in mild cases, but always increased in severe cases, ranging up to twice the normal. Two untreated cases showed the typical excessive lipemia, one with 2.9 per cent. and the other with 11.2 per cent. of fat in the plasma. Such lipemic blood looks like cocoa and the plasma like cream. Tyson's 1881 text-book and Joslin's 1916 text-book both devote the frontispiece to lipemia, the latter showing the appearance of the blood and plasma, the former depicting the fundus of the eye, for the condition is so marked that it can be recognized by intraocular examination. Normal urine contains a trace of fat, and this is increased in lipemia, Frugoni and Marchetti's case showing 0.088 per cent., Imrie's case 0.1 per cent., and Neisser and Derlin's case the unusual figure of 0.8 per cent. urinary fat.

For closer understanding, inquiry may be made first as to the nature of the fat circulating in such excess in these cases. Analyses

from Fischer to Bloor show that the great mass of it is neutral fat. Klemperer and Umber's claim that both lecithin and cholesterol are increased out of proportion to the neutral fat and their suggestion of the name lipoidemia instead of lipemia have been overthrown by more recent work. The lipoids are increased, but the higher the lipemia the greater is the predominance of the true fat. Imrie agrees with some earlier authors in finding lecithin relatively low in diabetic lipemia. Bloor has shown that lecithin varies somewhat in parallel with the total fatty acids until marked lipemia is reached, then falls markedly behind in relation to both these and cholesterol. The striking increase in cholesterol has been noted by authors from Fischer onward. In Imrie's case the blood contained 1.5 per cent. cholesterol. Bloor's case with 2.9 per cent. lipemia had 0.5 per cent. cholesterol and his case with 11.2 per cent. lipemia had 1.26 per cent. cholesterol. There is evidently a remarkable activity of cholesterol metabolism. The liver is generally bright yellow, but Fischer remarked that the liver cells did not contain large fat-drops as in ordinary fatty livers. The Kupffer cells like the endothelia elsewhere are stuffed with fat, and Kawamura found that this fat consists not merely of glycerides but cholesterol esters, which he claims the Kupffer cells normally refuse to take up. Jastrowitz undertook to study lipoid infiltrations in the fatty livers after various poisons. Beumer and Bürger described a case of diabetes in which an oat-cure cleared up the existing lipemia, but the cholesterol persisted at three times the normal figure. Klinkert states that the white spots in diabetic retinitis represent accumulations of cholesterol esters which may clear up considerably under treatment. The apparent thickening of the vessels of the fundus of the eye in lipemia is due to the opacity of the plasma and also to the cholesterol ester infiltration of their walls. Xanthomata are an expression of hypercholesteremia in diabetes as in other conditions, though other factors must be concerned. Von Noorden saw them clear up under treatment and return with aggravation of the diabetes. Bacmeister in one case furnished rather doubtful evidence that the cholesterol excretion in the bile may be markedly increased in diabetes. Of other compounds it may be noted that Imrie reported 0.38 per cent. of fatty acids present in the blood as soaps. Aside from the anemia-producing effects, fatty acids and their soaps are highly toxic, Munk finding that 0.11 to 0.13 gram oleic acid as soap injected intravenously in thirty to forty-five minutes suffices to kill rabbits by heart-block. Lipemic patients show no more anemia or intoxication than other diabetics, so it would seem either the findings of high percentages of circulating soap are mistaken or other substances present must protect against its poisonous action. In survey, therefore, it may be said that diabetic lipemia is characterized by an increase of lecithin, which becomes rela-

tively deficient as the lipemia becomes excessive; but comparison with other forms of lipemia is difficult, for it seems probable that if alimentary or any pathological lipemia could be raised as high as diabetic lipemia the relative deficiency of lecithin might be similar. Analyses on stuffed geese would be interesting. Diabetic lipemia is also characterized by a much greater increase of cholesterol, almost parallel with the fat, in excess of anything ever observed outside of diabetes, and in direct contrast to what occurs in alimentary lipemia.

Another contrast is seen in the corpuscles, for instead of the increase which occurs in alimentary lipemia, their fat content amid the tremendous lipemia of diabetes remains normal. Bloor finds the same to be true in other forms of pathological lipemia. The entire chemical picture is interpreted by Bloor as follows. The component which becomes more predominant as the lipemia increases is the true fat, which is the inert form of fat, and its accumulation indicates that the fat is not being properly prepared for assimilation. Likewise the relative deficiency of lecithin and the lack of fat in the corpuscles indicate that the corpuscles are not performing their function of transforming fat into lecithin, as in the earlier phase of assimilation. The high cholesterol figures are taken to mean that a later stage of the process is represented in this lipemia and that the cholesterol mechanism has not failed. Beumer and Bürger concluded that a considerable part of the cholesterol is free and not in esters, and in Imrie's case practically the whole of the cholesterol was found to be free. This fact might be significant if generally confirmed. Throughout it must be remembered that the entire subject is in the stage of hypotheses, but they are interesting as such and represent a real beginning in attacking the problem.

A second point for inquiry is the source of the fat in lipemia. In alimentary lipemia it is sufficiently obvious that the fat is derived from the food, but the lecithin, aside from what may come from the food, must be supplied by the body. In the various forms of pathological lipemia, lecithin and cholesterol must presumably be supplied by the body; this was certainly true in Müller's case of nephritic lipemia, in which the patient had been on lipoid-poor diet for months. In the anemic lipemia of rabbits, Boggs and Morris showed that the tendency to alimentary lipemia was increased, but yet the essential source of the blood-fat was the body-fat, for the lipemia developed on a diet of bread and grass, the animals rapidly lost weight, and in extreme emaciation the lipemia ceased. Because of the high lipoid content in diabetic lipemia, Klemperer and Umber concluded that the condition represents an increased breakdown of body cells, since only these could furnish so much lecithin and cholesterol. This explanation seems foolish when applied to a lipemia of 10 to 20 per cent. Several

authors have followed the hypothesis that the lipemia is derived from the body fat. Magnus-Levy has upheld the opposite view that the blood-fat is derived from the food, that the fat is taken up from the intestine and poured into the blood as usual, but there is some obstacle to its leaving the blood, either a physicochemical difference in the fat itself or a change in the cells or in the capillary walls; and that the huge quantities sometimes found in the blood may result from slow accumulation. Neisser and Derlin's patient with 19.7 per cent. blood-fat had very little body fat. They compared the iodin and Reichert-Meissl numbers of the fats in the food, chyle, blood, and several tissues and concluded that the blood-fat comes from the food. Imrie considered that the 300 grams or more of fat in the blood of his patient was too much to be derived from the food; the iodin number of 73 for the fatty acids of the blood compared well with 68 for the adipose tissue, but differed widely from that found in liver, heart, and kidney; he therefore concluded that the lipemia represents mobilization of connective-tissue fat. Bloor observed extreme lipemia only in two patients who had been eating excessive amounts of fat, while severe cases under treatment with restriction of fat as well as other foods seemed to show the tendency but the figures were moderate. Accordingly, he considered that the lipemia is derived from the food and is due to ingestion of fat beyond the capacity of a weakened assimilative function. It is to be regretted that very few fat determinations have yet been carried out on our patients at the Rockefeller Institute Hospital. The gross observations agree with the experience of Bloor and Joslin that even the most creamy plasma clears up under treatment. One extremely emaciated man showed a diminishing but still opaque lipemia through six days of fasting, which disappeared only gradually in the subsequent treatment. The exit of fat from the circulation must therefore be very slow in some cases. It should be considered a therapeutic duty to clear up a pathologic lipemia.

Dogs are subject to diabetic lipemia, as shown by an observation of Gerhardt mentioned by Naunyn, of 12.3 per cent. blood-fat in a dog with spontaneous diabetes and pancreas necrosis, which is the highest lipemia ever recorded in a dog. It is impossible for a dog to have more severe diabetes than that following total pancreatectomy, but the plasma generally is almost or quite clear. In an exceptional instance Seo observed lipemia of 2.4 per cent., with increase in lecithin and cholesterol. It is possible that Seo's dog was fat and that Gerhardt's dog had been eating fat. The facts perhaps indicate that the lipemia does not represent mobilization of tissue fat by the intense metabolic disturbance, unless to some extent in a fat-rich animal, but that on the contrary it mostly represents deficient assimilation of fat, and that depancreatized dogs with their maximal diabetes show little lipemia

because in them the deficiency in assimilation is balanced by the deficiency in digestion of fat.

This supposition can be tested in dogs of the type described at the outset, which have severe diabetes along with satisfactory digestive power. It is found that they are in fact subject to diabetic lipemia in its full intensity. These dogs have been fed suet, which is not the most easily or rapidly digested form of fat; but approximate determinations in our first case indicated lipemia rivalling that of Gerhardt. The tables show some values incidentally observed in connection with other work. Here is a sample of plasma from a child entering the Institute Hospital in coma. It contains 11 per cent. fat. The analyses made thus far show wide differences in the curves of fat in the blood of normal, phloridzinized, and diabetic dogs after identical feedings. The minor fluctuations will require further study, but the outstanding feature is the disproportionate increase in the diabetic animal. Granting severe diabetes, the lipemia varies largely with the digestive power. The record of Dog 396 (Table I) shows how the lipemia fell as the digestive power failed and the plasma became clear. These figures represent analyses twenty-four hours after feeding. On withdrawing fat from the diet lipemia clears up in from one to several days, according to its intensity, as seen in Dog 345 (Table III). A possible exception to this rule may occur in a type of fasting acidosis to be described later. In the terminal state of Dog 280 here depicted (Table II) gross observations gave the impression of an increase of blood-fat up to the development of a marked lipemia on fasting, but the opacity of the plasma was the only index, and this chance for a decisive verdict concerning the possible occasional origin of diabetic lipemia from body fat was lost through inability to carry out the necessary analyses.

The production of diabetic lipemia in dogs is a simple matter, but it opens opportunities. Here we have the means of flooding the body with fat in a manner unparalleled outside of diabetes, of making and unmaking this abnormality easily and quickly. The first result is the conclusive proof that the lipemia is derived ordinarily from the food-fat. It will be a simple matter to feed a variety of fats and compare with the blood-fat in the different cases; some information concerning fat assimilation may thus be gained, and we may be able to report such experiments later. But the simple fact that the lipemia appears so readily on feeding fat and ceases so promptly on omitting fat suffices to settle the dispute concerning its usual origin.

It is expected to publish later some analyses of the lipoid content of the blood and various organs, but this phase must be omitted at this time. As far as comparison is possible between Seo's analyses of liver tissue in diabetic lipemia and those of Jastrowitz and others of fatty livers produced by various poisons, no indica-

TABLE I.—DOG 396 (PARTIALLY DEPANCREATIZED).

Date, 1916.	Blood.‡						Urine.							Weight, kg.	Diet.	Remarks.
	Plasma sugar, %	Hb., %	CO_2, capacity.	Total acetone,* mgm. per 100 c.c.	Lipemia, qual.	Total fat, plasma %	Volume, c.c.	Total acetone,* mgm.	Sugar, gm.	Total nitrogen, gm.	Ammonia nitrogen, gm.	N : NH_3-N ratio.	D : N ratio.			
Aug.																
16–17	0.465	102	..	..	0	0.509	1313	761.6	50.55	24.10	1.97	12.25	2.10	..		
17–18	0.327	96	57.6	..	0	0.512	1358	614.8	59.70	22.80	..	..	2.62	11.16		
18–19	0.400	85	42.4	..	0	0.516	1430	344.9	58.40	25.40	2.58	9.85	2.30	10.90	1000 gm. lung.	
19–20	..	..	..	..	0	..	1290	443.8	71.50	22.60	1.74	13.00	3.16	..		
20–21	0.356	104	36.2	33.9	0	0.586	1220	873.5	67.20	23.80	1.83	13.00	2.82	10.80		
21–22	0.384	103	..	12.5	++++	1.752	410†	111.4	19.20	5.77	0.45	12.80	3.33	10.70		
22–23	0.324	98	46.2	29.0	++++++	1.600	804	405.2	24.92	11.58	1.35	8.52	2.15	10.82		Eats entire diet taking suet first.
23–24	..	..	..	..	..	..	985	425.5	26.35	11.20	1.88	5.95	2.35	10.86		
24–25	0.285	59	48.1	70.8	++++++	0.835	860	359.9	31.85	10.50	1.37	7.66	3.03	10.70		
25–26	..	..	..	..	..	..	915	786.9	19.08	11.30	1.10	10.30	1.68	10.80	400 gm. lung; 200 gm. suet.	
26–27	..	..	..	..	..	..	782	297.1	26.00	10.95	3.98	2.75	2.38	..		
27–28	0.268	39	32.8	97.8	+	0.445	1018	260.6	24.20	10.15	..	..	2.38	10.75		Growing weak; fatty diarrhea.
28–29	0.385	64	30.9	57.5	0	0.533	922	191.8	26.40	8.64	1.37	6.30	3.06	10.25		
29–30	..	..	..	..	0	..	720	123.8	30.00	10.30	2.74	3.76	2.91	10.20		Diet forced; vomited; 5 gm. sod. bicarbonate.
30–31	0.294	45	38.6	67.0	0	0.365	1020	..	24.40	9.50	4.40	2.16	2.57	10.17		
31–Sept. 1	..	..	..	..	..	..	938	..	24.10	6.60	3.00	2.20	3.65	..		Moribund; killed.

* Total acetone bodies as acetone. † Incomplete specimen. ‡ Blood drawn twenty-four hours after feeding.

TABLE II.—DOG 280 (SEVERE DIABETES).

Date.	Blood				Urine.					Remarks.
	Plasma sugar, %	Hb., %	CO_2, capacity.	Lipemia, qual.	Total nitrogen, gm.	Ammonia nitrogen, gm.	N : NH_3-N ratio.	Sugar, gm.	D : N ratio.	Diacetic acid.	
Aug. 11–12	..	..	..	..	3.07	0.930	3.30	6.35	2.07	+++++	
12–13	0.345	70	24.2	+++++	15.21	3.66	4.16	37.92	2.50	+++++	Fasting.
13–14	0.435	70	29.0	++++++	7.19	0.50	14.40	7.66	1.06	+++++	Bicarbonate. Death.

TABLE III.—DOG 345 (PARTIALLY DEPANCREATIZED).

Date.	Weight.	Blood.‡ Plasma sugar, %	Hb. %	CO_2 capacity.	Acetone, qual.	Lipemia, qual.	Total fat, plasma %	Urine.† Volume, c.c.	Acetone, qual.	Total acetone,* mgm.	Total nitrogen, gm.	Ammonia nitrogen, gm.	N : NH_2-N, ratio.	Dextrose, gm.	D : N ratio.	Diet. Remarks.
June 8	11.25	0.232	112	..	0	0	0.92	..	..	..	..	..	..	..	..	
9	..	..	..	..	0	++++	..	778	+++	43.6	6.900	..	..	70.79	..	
10	..	0.276	109	..	0	++++	3.88	880	+++	80.1	6.432	0.730	8.80	73.30	..	
11	..	..	..	..	..	..	..	835	++++	48.4	3.932	..	..	39.83	..	
12	10.5	0.228	110	..	?	0	2.42	562	++++++	25.9	3.844	0.612	6.26	43.27	..	200 gm. lung; 100 gm. bread; 100 gm. suet.
13	..	..	..	..	+	..	..	764	+++++	10.7	4.769	0.609	7.85	34.63	..	
14	..	0.213	108	50.0	+	+++++++	7.12	1270	..	58.4	5.092	0.531	9.58	65.65	..	
15	10.75	0.333	112	57.6	+	+++++++	6.00	940	++	..	5.038	0.394	12.80	64.95	..	
16	..	0.313	106	..	..	++++++	2.27	985	..	..	9.600	0.610	15.72	61.56	..	
17	..	..	..	..	..	..	..	990	..	..	6.672	..	..	61.87	..	
18	..	..	..	..	..	..	..	732	..	..	4.721	0.490	9.65	48.82	..	
19	10.85	..	..	..	..	..	..	1180	..	94.0	3.327	..	..	49.08	..	
20	..	..	..	..	..	..	..	598	..	35.9	2.738	0.203	13.42	44.35	..	200 gm. lung; 100 gm. bread; 150 gm. suet.
21	..	..	..	..	..	..	..	1370	..	..	5.918	0.479	12.38	59.59	..	
22	..	0.244	90	..	++++	++++++++	3.16	1810	+++++++	1042.6	5.249	0.796	6.60	78.73	..	Unwell.
23	..	..	..	..	..	..	..	1270	+++++++	812.8	6.731	0.792	8.50	68.58	..	
24	..	..	..	..	..	..	..	2090	..	1097.3	3.762	0.501	7.55	58.30	..	
25	..	..	..	..	..	..	..	915	..	657.8	6.405	0.602	10.66	67.71	..	
26	..	0.238	93	38.5	..	+++	3.79	590	+++++++	367.0	4.838	0.489	9.88	40.45	..	100 gm. lung; 100 gm. bread; 100 gm. suet.
27	..	..	..	..	..	..	..	804	..	313.6	3.939	0.426	9.26	64.32	..	
28	10.82	..	..	..	..	..	..	1285	..	..	4.011	0.552	7.26	75.68	..	Unwell.
29	..	..	..	..	..	..	..	620	..	282.7	2.852	0.303	9.40	47.74	..	
30	10.65	0.213	96	40.4	..	+++	..	690	+++++++	298.1	3.008	0.324	9.26	43.20	..	
July 1	..	0.222	97	..	++	+++	..	396	..	182.1	7.680	0.760	10.10	30.50	3.97	600 gm. lung. Improving.
2	..	..	..	..	..	..	..	608	..	307.8	12.800	1.137	11.21	35.90	2.80	
3	..	..	..	..	..	..	..	332	+++++++	127.2	8.370	0.713	11.78	23.90	2.86	
4	..	0.270	109	34.2	++	+++	1.53	636	..	359.3	16.250	0.850	19.11	30.60	1.88	
5	..	0.256	94	43.9	..	..	0.78	405	..	..	9.450	0.940	10.10	31.20	3.30	
6	10.3	0.323	90	36.1	..	0	0.90	830	+++++	192.6	16.600	1.930	8.60	51.90	..	
7	..	0.250	86	39.1	+	0	..	728	+++++	180.2	9.770	..	..	47.10	..	600 gm. lung; 100 gm. bread. Good condition.
8	..	0.357	86	47.7	..	0	..	1585	+++++	518.3	14.300	1.100	13.00	106.20	..	
9	..	..	..	..	..	..	..	1600	++++	488.0	15.400	..	..	94.40	..	
10	10.13	0.304	86	46.4	+	0	1.98	2025	++++	559.0	10.400	1.010	10.30	93.10	..	

* Total acetone bodies as acetone. † Not catheterized. ‡ Blood drawn twenty-four hours after feeding.

tion is offered of any specific chemical character of the organ infiltration in diabetes. The huge amount of circulating fat and the remarkable activity of lipoid metabolism offer other opportunities which we shall not be able to follow up. The unusual quantities of cholesterol that seem to be formed invite a study of the excretion in bile and feces and other features important to those interested in cholesterol metabolism. Various problems lately under investigation by authors such as Aschoff, Landau, Mulon, and Borberg concerning the morphology and the chemistry of fats and the function of the adrenal cortex and other organs in regard to them may perhaps be studied with special advantage in a condition in which the lipoid metabolism is specially disturbed or exaggerated.

The metabolism of matter and energy has never been studied in human patients with extreme lipemia, and to avoid confusion from acidosis or other factors it is desirable to make a series of comparative observations on the same individual in the lipemic and non-lipemic condition, and this can be done most conveniently in animals. All are now familiar with the work in Lusk's laboratory, which has shown that the combustion of any food is increased as the supply of it to the cells is increased. Ingestion of any food increases the total metabolism more or less according to the kind and quantity of the food. Ingestion of fat causes alimentary lipemia and the combustion is preëminently of fat. Bleibtreu's geese, stuffed with rye, with lipemia up to 6 per cent., are said to have shown respiratory quotients as high as 1.33. Whether the figures are strictly correct or not it seems evident that values above unity were present, indicating combustion preëminently of carbohydrate and the formation of fat from carbohydrate. This means one of two things: either the carbohydrate or the general plethora inhibited the combustion of fat in spite of 6 per cent. fat in the blood—in which case Lusk's law of summation of stimuli is reversed—or if there was combustion of fat in the remotest degree proportional to the lipemia the total metabolism or the formation of fat from carbohydrate must have been tremendous. Interesting modifications of this experiment might be made by giving fat-rich instead of carbohydrate-rich diet or by using partially depancreatized geese. It is well known that in diabetic patients or animals alimentary hyperglycemia is more pronounced than normal, but the effect on the respiratory quotient is less, and in severe cases may be absent altogether, and this is one of the best evidences of deficient combustion of carbohydrate in diabetes. The case with fat is different, for diabetic patients and even totally depancreatized dogs always burn fat readily. The distinction is not absolute, for depancreatized birds—chickens, ducks, geese—show intense hyperglycemia with little or no glycosuria and can even receive considerable carbohydrate by feeding or injection and

dispose of it somehow. Their kidneys are highly impermeable to sugar, but there is a difference beyond this, for feeding or injection of sugar in severely diabetic dogs with renal impermeability means rapidly fatal hyperglycemia—possibly 2 per cent. blood-sugar. The diabetic birds do not metabolize their carbohydrate normally, for glycogen is deficient and emaciation and death occur. The mammalian kidney is almost impermeable for fat, so that lipemia cannot be checked by excretion, and the presence of acetone bodies indicates some abnormality in fat combustion. But the known abnormality consists merely in incompleteness in the end products; no experiments have ever indicated any difficulty on the part of the diabetic in attacking the fat molecule. Patients and suitable diabetic animals often go along on a certain level of marked hyperglycemia, without glycosuria, and evidently burning some carbohydrate. They seemingly require a higher "pressure" of sugar in the blood in order to accomplish the combustion of sugar. In the moderate hyperlipemia ordinarily present in severely diabetic patients, Bloor saw evidence of a similar need of increased fat "pressure" in the blood in order for the cells to burn fat. There is opportunity to test this idea with respiration experiments. In contradiction to the prevalent belief of normal fat assimilation in diabetes, investigation will probably show that a certain level of lipemia does not have equal metabolic influence in non-diabetic and in diabetic lipemic conditions. It will very likely be found that the effect on the gaseous exchange is slower and of less degree in diabetic lipemia, corresponding to the known facts concerning hyperglycemia in the milder cases, so that an alimentary lipemia of 2 or 3 per cent. in a normal animal may represent a greater activity of fat metabolism than much higher blood-fat values in an animal with diabetic lipemia. Also, it may be found that the metabolic effect varies among diabetics in proportion to their susceptibility to lipemia, and conceivably may not be fully normal in any severe diabetic. Studies of this sort will throw light on the ability of the diabetic to attack the fat molecule; they may help to show why fat-feeding seems sometimes neither to strengthen nor build up a patient; they will indicate what significance may be assigned to lipemia in the question of metabolism in diabetes; and by completing the proof that lipemia is due to deficient assimilation rather than increased mobilization of fat (even if increased mobilization sometimes occurs), they may contribute an analogy in support of the dominant belief that the hyperglycemia is primarily due to deficient assimilation rather than increased mobilization of sugar.

Our investigation of lipemia by the use of diabetic dogs to date has dealt chiefly with the problem of the actual cause of it, its relation to other diabetic phenomena and to the internal function of the pancreas, and the information which it may furnish concern-

ing the fundamental diabetic condition. Besides the origin from food-fat, certain other questions can now be definitely answered.

First, the visible fat is not in the abnormal form insoluble in ether. Seo found in his one case that the opacity was cleared by ether, and the same has been our experience.

Second, the power of plasma to hold fat in clear solution is not diminished. In connection with the hypothesis of combined sugar, I formerly suggested a possible analogy with fat, in that lipemia might be due to deficient combination of the fat, and raised the question whether the pancreas supplies anything of importance for this combination. Reicher determined the fat before and after digesting blood with pepsin-hydrochloric acid, and concluded that the latter fraction has no importance. Seo mentioned visible lipemia in only one of his depancreatized dogs, yet the blood-fat in the other instances was from 1 to 1.5 per cent. This might indicate an unusually high power of the plasma to hold invisible fat, and the same possibility seems indicated by some of our experiments, and would not be surprising in view of the high lipoid content. Accordingly, no significant reduction in the simple ability of the blood to "mask" fat has been demonstrated. On the other hand, Bloor's belief is that fat must be combined into lecithin in order to be assimilated, and that a deficiency of this combining function is present in diabetic lipemia. The facts at least suggest that methods used for testing the combination of either fat or sugar should not be too crude.

Third, the relation of fat in plasma and corpuscles is of interest especially in connection with Bloor's hypothesis. Unfortunately most of our determinations so far have had to be limited to the plasma, and only a few analyses of corpuscles have been made. Thus far they indicate low total fat content in the corpuscles. Having controllable experimental conditions, it should be possible to trace any significant alterations from the normal through the mildly lipemic animals to the extreme degree in the severely lipemic animals. This research is in progress, but it is better to omit discussion at present rather than attempt conclusions from insufficient data.

Fourth, lipemia is not due to hyperglycemia. For example, mildly diabetic animals, even with abundant fat in the diet, may be made to show extreme hyperglycemia without corresponding lipemia.

Fifth, lipemia is not due merely to absence of carbohydrate or loss of sugar from the body. Maximal phloridzin poisoning with feeding of nothing but fat, or the longest possible phloridzination on diet free from carbohydrate and high in fat, has failed to produce in dogs anything resembling diabetic lipemia.

Sixth, lipemia is not due to the presence of acetone bodies. Lipemic patients generally have acidosis, but a case of lipemia

without ketonuria was described by Beumer and Bürger. It is well known that many patients with severe acidosis and even coma show clear plasma. Bloor found "no definite relation between high blood lipoids and the occurrence of acetone bodies in the urine." In dogs it can be shown that the acidosis of phloridzin poisoning causes nothing like diabetic lipemia, that diabetic acidosis may occur without lipemia, and that marked lipemia may be present without acidosis. Maximal lipemia probably never exists without acidosis, but this is because acidosis goes with the general severity of the diabetes.

Seventh, lipemia is not due to change in the reaction of the blood. The greatest possible reduction of the carbon dioxide capacity by diabetes, phloridzination, or chronic hydrochloric acid poisoning has produced none of the characteristic lipemia.

Eighth, lipemia is not due solely to removal of pancreatic tissue within the limits mentioned. If enough pancreatic tissue is removed to produce even severe diabetes, but the actual occurrence of diabetes is avoided by diet, the characteristic lipemia does not occur. In some such cases alimentary lipemia certainly persists longer than normal, but this may represent merely a slower digestion of fat owing to the smaller supply of pancreatic juice. If the curve of the lipemia is lower as well as longer, it will indicate such delayed absorption. The characteristic of diabetic lipemia is that it both rises higher and falls more slowly than normal. When the assimilative disturbance is slight it may to some extent be balanced by the delayed absorption, so that the mere prolongation of slight lipemia becomes hard to interpret. These experiments are in progress and a sufficient number are not yet finished to permit positive conclusions. But it is certain, as stated, that the full diabetic lipemia never occurs in the absence of other symptoms of active diabetes.

Ninth, lipemia is not the result of breaking down of a hypothetical "fat function" by direct overstrain of that function. Here again tedious experiments extending over months have been involved. These experiments have proved that the heaviest and most prolonged fat diets, in normal and partially depancreatized animals, neither increase nor diminish the susceptibility to lipemia. If the conditions are such that the fat-feeding give rise to glycosuria and acidosis the lipemia begins to mount up; otherwise not.

Tenth is the question of the relation of lipemia to the severity of the diabetes. Up to the time of the present treatment which restricts fat in the diet, high lipemia has been considered a sign of very bad prognostic import. Bloor found some elevation of blood-fat in all severe cases, normal or subnormal values in mild cases. Beumer and Bürger have reported the only known instance of lipemia in mild diabetes. In dogs of the type described above, it is easy to show that the lipemia depends upon the severity of the

diabetes. The partially depancreatized dog, with relatively little tendency to lipemia as long as he is kept free from diabetes, acquires the marked susceptibility without any further operation as soon as severe diabetes is brought on by overfeeding with any kind of food. The most striking experiment is to keep the plasma continuously clear by carbohydrate or protein diet, then suddenly give a meal of fat. High lipemia is present within a few hours and persists for more than twenty-four hours. On continuance of fat diet the lipemia mounts to a point governed by the digestive power. As in human cases it is then unremitting, and like an old hyperglycemia, varies relatively little with meals. With breakdown of digestion, or on withdrawal of fat from the diet, the lipemia clears up in from one to several days, according to its intensity. The tables already referred to illustrate some of these statements.

This permits discussion of the relation of lipemia to the internal pancreatic function. There may be three possibilities: Is lipemia due to disorder in some organ or in the general system secondary to the original diabetic disturbance? is it another manifestation of deficiency of the same hormone concerned in carbohydrate metabolism? or does it represent lack of some different internal secretion of the pancreas? There is sound justification for speaking of several internal functions of the pancreas. Diabetes is not a mere glycosuria or inability to assimilate glucose. There are abnormalities in the metabolism of protein, fat, and doubtless of mineral substances which are primary and cannot be reproduced secondarily by phloridzin or any other means. But it is possible that the various functions in question all belong to one internal secretion, and this unitarian hypothesis is inherently the most attractive one. It is a plausible view that the pancreas supplies something necessary for the synthesis and maintenance of protoplasm, that deficiency of this factor makes nutrition of the cells difficult and disposes to breaking down of their reserves, and that this tendency makes itself felt in regard to all classes of foods, but earliest and most manifestly in regard to the most labile and most easily excreted forms. Only positive evidence could justify a doctrine of plurality of internal secretions of the pancreas. The unitarian standpoint would have theoretical importance, for it might reasonably be inferred that the part played by the single hormone would be similar toward the various classes of foods. Glycosuria and non-assimilation of carbohydrate—lipemia and acidosis—increased protein catabolism, aminosuria, and changes in the creatin-creatinin relation—diabetic edema and other anomalies concerning salts, all afford different lines of approach. If all alike are due to deficiency of a certain action of a single hormone, comparisons will aid in learning what the action of this hormone is, and by following the different trails it may be possible to track the thing

home and master the secret of the internal pancreatic function and diabetes.

Between the partially depancreatized animal without diabetes or lipemic tendency, and the same animal after feeding has brought on severe diabetes and susceptibility to lipemia, there is only one known anatomical difference, which consists in exhaustion and degeneration of cells in the islands of Langerhans. The fact that this alteration and the lipemic tendency come on simultaneously, and are typically produced by pure carbohydrate or protein feeding, proves conclusively that the disorder underlying lipemia is bound up to considerable extent with the other diabetic disturbance and is not entirely independent. Possible evidence for the existence of more than one internal pancreatic secretion might be found in the discovery of Lane and Bensley that the islands of Langerhans consist of two different varieties of cells, filled with granules which stain differentially; these cells are believed to be independent in origin and type and not transitional or derivable one from the other. This histological interpretation is strengthened by Homans' discovery that only the so-called Beta cells ordinarily degenerate in experimental diabetes, while the Alpha cells remain preserved even in advanced stages and show particularly dense granulation. This observation was confirmed in the work at this Institute. But it might still be possible that both types of cells are concerned merely in carbohydrate metabolism. Krumbhaar published the description of an important case of spontaneous diabetes in a dog in which the pancreas was about twice the normal size and its tissue appeared normal; and microscopic examination showed advanced degeneration of the Beta cells everywhere, along with less extreme but still marked exhaustion of the Alpha cells. Lipemia or acidosis was not found in this animal, but it apparently was not studied on fat diet. Martin has discovered that some of our experimental dogs show this same degeneration of the Alpha cells. He is following up the investigation, but there has not yet been time for enough comparisons to establish the possible significance. When a dog shows a dextrose-nitrogen ratio equal to that following total pancreatectomy, it will be interesting to know whether the Alpha cells are degenerated or not. If they are intact their part in carbohydrate metabolism will become very questionable. Material is available from animals of different species, different ages, different grades of intensity and duration of diabetes, on various diets, in nutritive states ranging from obesity to emaciation, with lipemia and acidosis present or absent, and with other physiological or pathological variations, so that it may be possible to throw some light on the function of the Alpha cells and the unity or plurality of the internal pancreatic secretion.

The facts concerning human patients must also be considered in

this connection, and the question whether the full conditions are reproduced in dogs. Granting that all patients with severe diabetes have some tendency to lipemia, is this tendency equal in all of them? When the majority of cases show fairly clear plasma, and a small minority show lipemia of 10 to 20 per cent., can it be maintained that varying quantities of fat in the diet suffice fully to explain such differences? If there is another cause for the discrepancy, does this cause consist in some additional pancreatic disturbance, or in a breakdown in some other organ or in the general system? It is unfortunate that accurate observations covering this point have not been made; but probably most physicians who treat diabetes will have the decided impression that individual variations exist, and that the majority even of severe cases on heavy fat diet are not subject to the most intense lipemia. Though it is difficult to gauge the true severity of diabetes, possibly Beumer and Bürger's patient above mentioned manifested a special susceptibility to lipemia in the presence of only mild diabetes. Several of the patients at the Institute have shown intense lipemia, and it is not evident that their condition was more severe or that they had eaten more fat than some others without lipemia. Certain patients under treatment were tested with heavy fat diets for other purposes and remained free from lipemia. On the other hand a very few incidental observations seem to indicate that when there has been heavy lipemia, and when it and the glycosuria have been recently cleared up, a meal of fat may cause the plasma to remain turbid for more than twelve hours. The suggestiveness of these chance observations is strengthened by the experience with dogs, in which such a phenomenon certainly occurs. It may prove worth while to investigate whether patients react differently to such a test and whether it signifies a specific weakness of fat assimilation.

Certain observations seem to indicate that in dogs the tendency to lipemia may vary independently of the other diabetic symptoms, and that the governing conditions are at least in part experimentally controllable. The work in progress must be carried further before it will be possible to decide positively concerning such observations or interpret their significance for the theory of diabetes. The gist of the matter to date is that diabetic lipemia has been reproduced in dogs, and there are hopes that the possible varying grades of susceptibility shown by human patients may be experimentally imitated.

II. Acidosis.

The second subject for discussion in connection with the role of fat in diabetes is acidosis. Here the primary requirement for clearness is a definition, and the one adopted may be said to rest on three bases.

The first of these is origin and general usage. The pioneer workers of the Naunyn school grasped this problem broadly and deeply; they did the principal work that has been done, and they marked out the fundamental lines which all subsequent research has followed. Hallervorden recognized the significance of the increased ammonia. Stadelmann attributed coma to acid and suggested alkali therapy; it is noteworthy that he used in this connection the term acid intoxication, not acidosis. Minkowski perceived the presence and meaning of the diminished carbon dioxide content of the venous blood. Magnus-Levy determined the balance of acids and bases in the urine. But Naunyn introduced the term acidosis, and said, "With this word I designate the formation of β-oxybutyric acid in metabolism." The name and definition received general adoption, and have been used also by the opponents of the Naunyn school who believe that the intoxication and coma represent something other than a simple shift of reaction. The more recent followers of Naunyn should not pervert his definition, which has been acceptable to both parties; and even if the word must become the exclusive property of either faction, it is not for the losers to carry off the nomenclature.

The second basis of definition is that of need and distinctiveness. Diminished alkalinity, increased hydrogen ion concentration, lowering of carbon dioxide, decrease of buffer salts, and (for the symptoms of these changes) acid intoxication—all these terms have definite meanings, and to appropriate the name acidosis for any one of them is merely to create a useless synonym. No other name but acidosis exists for the metabolic process which it denotes. Ketonuria and ketonemia have their accurate place but do not cover the ground. Possibly the word ketosis might be suggested and used for special purposes, but the change of established usage would be difficult and seems unnecessary. It may be urged that there are states of increase of other acids, lactic, phosphoric, etc. If desired it may be feasible to include these under a broad interpretation of acidosis, and to distinguish them when necessary from acetone body or diabetic acidosis. But the latter is the original and most important type, and the name acidosis belongs preëminently to it.

The third ground for the definition is its fundamental significance. Here may be seen the sound judgment of Naunyn in defining on the basis of metabolism, not of reaction. A definition must be qualitative not quantitative. Criteria of reaction vary with the tests; the finer methods of today reveal changes not formerly perceptible, and future technic may give truer appreciation of the physiological balance in the blood or may follow changes into the cells. But the metabolic disturbance in question is continuous and must be regarded as a unit. It is recognizable at a time when the protective mechanisms of the body are apparently efficient to prevent any abnormality of reaction, and it persists in spite of any dosage of alkali. Furthermore, a comparison with

typhoid fever is illustrative. Fever is a prominent feature in typhoid infection and has been embodied in the very name of the disease. Also, simple hyperpyrexia is a possible cause of death, and rightly or wrongly many physicians believe that they benefit patients and even save lives by treating this symptom with cold bathing or other measures. Nevertheless, the proper definition of typhoid fever must be in terms of infection with Bacillus typhosus and not in terms of fever. Similarly, the acid character of the products in acidosis is important and has received recognition in the name of the condition. Simple displacement of reaction may be a cause of intoxication and even death, and clinical improvement and even the saving of life may be achieved temporarily by the mere administration of alkali. But the metabolic disturbance back of it all is the real thing to be defined and comprehended and treated. A slight objection might conceivably be raised on the basis of rare cases of reported coma without acetone bodies. But there is the old-time answer that such cases though occurring in diabetes may not be diabetic coma; and there is no evidence that a definition based on reaction would fit them any better. For these reasons it seems best to retain the definition of acidosis in the original sense of Naunyn—namely, as that state of metabolism of which the presence of abnormal quantities of the acetone bodies is the one known constant characteristic.

This leads to the question of the origin of the acetone bodies. Their appearance was first ascribed to fermentation of carbohydrate, then to breakdown of body protein. More recent experiments with phloridzin and liver perfusions prove the possibility of a partial derivation from the leucin, tyrosin, and phenylalanin of the protein molecule, while the greater portion of the amino-acids form glucose, and the exact status of some of them is uncertain. But the work of Rosenfeld, Hirschfeld, Geelmuyden, Magnus-Levy and others made it apparent that the principal source of the acetone bodies is fat. The disposal of fat up to the point of its leaving the circulation and entering the cells was discussed under lipemia. Aside from storage its fate in the cells is supposedly combustion proceeding through successive carbon groups, the best accepted chemical view being the beta-oxidation hypothesis of Knoop, according to which butyric and β-oxybutyric acid may be normal intermediary products and excretion of the latter may represent merely imperfect combustion. One molecule of higher fatty acid could thus furnish only one molecule of β-oxybutyric, and Magnus-Levy calculated that the quantity thus available corresponds to the maximum known excretion, but that in some cases this demands a molecule of acetone bodies from practically every molecule of fat burned. Acetone is a secondary and chiefly abnormal product, but there is a question which of the other bodies is primary. Formerly, diacetic acid was believed to be

derived from β-oxybutyric by oxidation, but Maase, Blum, Dakin, and Marriott have brought evidence that the reverse may be true and that diacetic acid may be the primary product formed from butyric and β-oxybutyric be derived from it by reduction. The orthodox belief is that all cells, including muscle cells, burn fat directly. Von Noorden is one of the very few who imagine that the muscles can burn only sugar, which the liver forms from fat for their use, and that acetone body production is associated with the formation of sugar from fat. It is a common belief that the acetone bodies are produced largely or chiefly in the liver. In Embden's laboratory, perfused livers have been shown to form acetone, while kidney, lung, and muscle formed none; furthermore, the livers of depancreatized and phloridzinized dogs formed several times as much acetone as those of normal dogs. Also, Fischler and Kossow phloridzinized Eck-fistula dogs and found that these animals, with ligation of the portal vein and drainage of the portal blood directly into the vena cava instead of through the liver, showed less ketonuria than ordinary dogs likewise receiving 1 gram of phloridzin daily; but with the reversed Eck-fistula, that is, with ligation of the vena cava and drainage of its blood together with the portal blood through the liver, the ketonuria was increased above that of the controls. The experimental evidence thus seems strong, but it requires criticism. It would be well if more work were done along the lines of Fischler and Kossow, to learn whether their results are significant or accidental or whether any other conclusion is possible. Too much importance must not be attached to perfusion experiments or to the milligrams of acetone formed. It may well be conceded that liver cells are able to form acetone, also that acetone formation is more active in depancreatized and phloridzinized than in normal animals. But the negative experiments with muscle and other organs do not prove that they are unable to form acetone bodies or that the quantity which they form is small. For example, authors have reported that the liver perfused with glucose forms glycogen, but no one has demonstrated the formation of glycogen when muscles are thus perfused, and it is certain nevertheless that muscles in the living body form much glycogen. The function of the liver is primarily metabolic; perhaps for this reason it gives more positive results on perfusion than other organs in which the metabolic is subsidiary to other functions. At any rate the reason for the close scrutiny of these experiments lies in their disagreement with the chemical views of fat metabolism above mentioned. It would seem that only in the tangled field of diabetes could writers put together such doctrines as the predominant production of acetone bodies in the liver and the chemical views of Magnus-Levy and Knoop, with no consciousness of conflict. If there is anything like the excretion of one molecule of acetone bodies corresponding to each molecule of fatty acid

burned, and if it be claimed that any large proportion of the acetone bodies arises in the liver, it follows either that the liver is burning this same high proportion of the fat, or else that the muscles are burning part of their fat perfectly while the liver is breaking up individual fatty acid molecules into several molecules of acetone bodies. Von Noorden's hypothesis is at least consistent on this point. But if, according to the accepted belief, cells in general attack the fat molecule directly, then acetone bodies are formed where the combustion occurs. In Woodyatt's metaphor, the engine "smokes" with acetone bodies. And since the great preponderance of combustion is in the muscles, it follows that the predominant formation of acetone bodies is in the muscles. The only escape would be in an improbable assumption that the muscles burn fat to a certain point and that hypothetical products are conveyed from them to the liver to be formed into acetone bodies. The proof for the chemical theories is not absolute, but it seems stronger than that for the origin of acetone bodies in the liver. Therefore, the most probable view at present is that the formation of acetone bodies takes place mainly in the muscles and other organs and only to a minor extent in the liver.

It is impossible in the present space to review the literature of acidosis or even the literature of fat-feeding, which more directly concerns the present topic. It is well known that fasting human beings regularly show ketonuria. It is not generally appreciated how widely this phenomenon varies even in supposedly normal persons. Waldvogel and Brugsch observed instances in which fasting produced only trivial acetone excretion. Benedict's fasting man, eliminating approximately 2 to 7 grams of acetone bodies daily, may be considered a fair average. The upper extremes are represented in reports by Von Noorden of excretion of 48 grams in three days of fasting by a girl with gastric ulcer, by Bönniger and Mohr of excretion of over 24 grams in one day by a fasting woman, and by Gerhardt and Schlesinger of 40 grams daily in hysterical vomiting. The available store of body fat is one important factor, and Folin and Denis published a recent illustration of marked acidosis with symptoms in fasting obese women. But it is not certain that this is the sole variable, and only a large statistical study could show whether normal persons of similar nutrition have inherently different susceptibilities to acidosis. Ketonuria likewise results from simple carbohydrate abstinence, and fasting ketonuria is increased by protein-fat diet. Protein is considered antiketogenic in normal persons, the glucose-forming amino-acids prevailing over the others. Evidence that it may give rise to ketonuria has been offered by Rosenbloom and Hurtley for diabetic patients and by Kirk for depancreatized dogs. Such an effect is possible through loss of the carbohydrate portion leaving the ketogenetic portion, through a simple stirring up of metabo-

lism and elimination (just as a submaximal D : N ratio in a fasting depancreatized dog may rise to maximal on feeding), and, in human patients, probably through aggravation of the essential diabetic process. In line with this, a high protein diet is inadvisable for the average patient threatened with coma. Fat constitutes the essential dietary cause of ketonuria in normal persons; for example, Landergren and Forssner thus produced excretion of some 40 grams of β-oxybutyric acid. Attempts have been made to establish the quantity of carbohydrate requisite to prevent acidosis, the figures generally being set at 50 to 150 grams. Geelmuyden found that more, perhaps 200 grams, might be necessary to abolish an existing acidosis, also that the quantity required varies with the quantity of fat in the diet. Zeller worked out a law that for prevention of acidosis one molecule of sugar must burn for each two molecules of fat, which means the ingestion of one part of carbohydrate for four parts of fat. Von Noorden and his followers have emphasized the wide discrepancies between different diabetics as respects the relation between carbohydrate assimilation and acidosis: for example, Mohr's comparison between two patients under similar conditions, one of them excreting less than 1 gram of β-oxybutyric acid and the other over 15 grams, and his records of other patients with abundant ketonuria while assimilating 120 to 150 grams of carbohydrate. But Mohr mentions a similar discrepancy between two non-diabetics, and Forssner excreted 33 grams of β-oxybutyric acid with 40 grams of carbohydrate in his diet. Gigon tabulates the Landergren and Forssner experiments to show that individual idiosyncrasy is as marked among non-diabetics as among diabetics. It is well recognized, as shown in experiments of Reich quoted by Rosenfeld, that an initial ketonuria generally diminishes on continuance of the same diet. This behavior of normal persons is usually shown by diabetics who do well, and Mohr states that obese persons respond similarly. Folin and Denis observed that repeated fasts in obese subjects produce, so to speak, an "immunity" against acidosis, and the same has been noticed a number of times in our diabetic patients. A minority of diabetics develop serious acidosis on fasting, but when a short period of suitable diet, even protein-fat diet, is interposed no case has yet been encountered in which a second fast was not well borne. On the other hand the Landergren-Forssner experiments give no indication of any such "immunity" to excessive fat diet. The great lack is of normal data. The Eskimos are much talked about but have never been studied. It is really unknown to what extent the normal human organism can accommodate itself to fat combustion or what proportion of protein or carbohydrate is the minimum necessary permanently to prevent acidosis. Some interesting acetone and ammonia figures ought soon to become available from severely diabetic patients who are kept free from

glycosuria for long periods on diets low in protein and carbohydrate. The fat tolerance in such patients seems to differ widely. The susceptibility to acidosis may perhaps also be governed partly by variables such as the age or the level of nutrition, whether high or low. Even under identical conditions the attempt to establish a universal rule on this point promises to be fruitless, for the reason that the widespread belief regarding acidosis as governed solely by a supposed ratio between fat and carbohydrate in combustion is incorrect. The existing evidence against it may be summarized as follows: (1) the seemingly constitutional idiosyncrasies manifested by both diabetic and non-diabetic individuals, shown in the literature; (2) the acidosis in certain infections, intoxications, liver necroses, and in the cyclic vomiting and gastro-intestinal crises studied by Howland and Marriott and others in which deficiency of carbohydrate seems an inadequate explanation; (3) the acidosis which Taylor produced in himself by an ash-free diet of seventy-odd grams of protein, 120 grams of fat, and 200 grams of sugar. It is well for those who think of acidosis as necessarily due to lack of carbohydrate to bear in mind this well-authenticated case in which it was produced by lack of salt on a diet adequate in protein, moderate in fat, and liberal in carbohydrate. Rumpf and Joslin's idea of the importance of salts for threatened coma may find an analogy here. The fact that salt starvation has not had this effect in other such experiments perhaps adds to the evidence of personal idiosyncrasy. The experiment might bear repetition in subjects presumably disposed to acidosis, as the obese.

Notwithstanding that fat ingestion has been proved to create or increase ketonuria in both normal persons and diabetics, fat has remained the one unrestricted food in diabetes. Even Forssner saw reasons to justify the prevailing treatment, considering that tolerance for fat is acquired, that its addition to protein then increases ketonuria by only a few grams, and that its use is preferable to undernutrition. Naunyn, von Noorden and all others have agreed that fat should be withdrawn only in the presence of threatened coma. The few writers who have advocated occasional restriction of fat have merely favored limiting it to the caloric requirement of a maintenance diet. The more common practice has been to push fat by all possible devices to the utmost limit of the digestive power, with the idea of building up strength and nutrition. Another support for the fat diet was given in the statement that the heaviest fat feeding only slightly increases the combustion of fat, the surplus being stored. In this connection the question arose why then ketonuria should be increased by fat ingestion, and various authorities inclined to the view that food-fat may somehow behave differently from body fat in metabolism. Murlin and Lusk proved that six hours after taking 75 grams of fat a dog's heat production may be 30 per cent. above the basal.

The protein-sparing power of fat is known to persist in diabetes. Therefore the absolute and relative increase in fat combustion now appears a sufficient explanation of the slight increment of ketonuria following any single fat meal, and the summation of such effects presumably accounts for the results of longer feeding, so that there is at present no evidence of a metabolic distinction between food fat and body fat. The relief of diabetic acidosis by fasting is doubtless due not only to diminished combustion of fat but also to a beneficial effect of undernutrition upon the assimilation of all classes of food. The fact that patients with severe diabetes frequently become almost free from acidosis, under the circumstances which give rise to a very appreciable acidosis in normal or mildly diabetic persons, would not appear so paradoxical if we had adequate information concerning the reactions and accommodations of normal subjects under truly comparable conditions. The diabetics merely demonstrate a reserve power in the human organism which normal persons could doubtless bring forth under an equal stimulus. Typical of the former treatment of diabetes has been the period when the patient was evidently developing this power and becoming able to live on protein-fat diet with little or no ketonuria; then the later period with heavy ketonuria, whether sugar-free on strict diet or glycosuric on mixed diet, and the necessary end in coma. The moral is that the natural or reserve powers of assimilation should be protected in treatment and should not be broken down by overfeeding with fat or any other food. The material for clinical experiments heretofore has comprised either fairly mild cases or severe cases with the usual heavy and fluctuating ketonuria. The tests under these conditions have failed to reveal the insidious and cumulative injury caused by fat. When severe cases are made free from glycosuria and ketonuria, a material is afforded upon which any careful clinician can convince himself of the harm of excess of fat. Washing butter to remove traces of lower fatty acids while overwhelming the system with fat which must necessarily be katabolized into lower acids is one of the absurd practices of past treatment now abandoned. And finally it is to be noted that severe cases kept alive for months or years on low protein and carbohydrate, with glycosuria and acidosis kept up essentially by fat, are the cases that offer the greatest difficulty for successful treatment or for building up a tolerance for any kind of food.

It is important to extend research on acidosis to species other than man. A really satisfactory reproduction of the human condition is one of the greatest needs, for the very sake of the knowledge of how to produce it, and also for the opening up of a subject which always comes when it is made susceptible to animal experimentation. It is also desirable to study this disorder in species which do not so closely imitate man, because in man certain fea-

tures are found quite regularly associated, and are generally conceived as belonging together, and it is valuable to learn whether this association is inevitable, and if not, to take such an opportunity to study the individual factors thus separated. There is no known laboratory animal which reacts precisely like man in this respect. Some apes or monkeys may be expected, according to Baer's findings, to show fasting ketonuria; but the large ones are too scarce and expensive, the smaller ones lack stamina, and it is doubtful if any of them can meet the requirements of appetite and digestion. Other species, as a rule, show ketonuria neither on fasting nor on protein-fat diet. A distinction is generally held between carnivorous and other animals, presumably on the assumption that animals accustomed to carbohydrate will have difficulty in burning fat without it, and on a vague generalization of the observations that dogs and cats are less easily subject to acidosis than man. The first thing learned in studying a variety of species is that this distinction is wholly mythical. There are differences between species but none between classes of animals. Baer observed that herbivora are as immune to fasting ketonuria as the carnivora. He reported ketonuria in a pig on fasting but not on protein-fat diet. A pig which we studied at the Institute proved more resistant to ketonuria than any dog; and persons who may have cherished a secret objection to being classed as the metabolic brothers of the omnivorous pig may be gratified by our experience that no other mammal reacts less like man. On the other hand the typically carnivorous badger shows ketonuria, which in diabetes begins almost simultaneously with the glycosuria. The dog is the best and most human of animals in the laboratory as elsewhere. He talks with his eyes and tail instead of his tongue, and there are some metabolic differences of similar degree. But he has told us so much of what we know about diabetes that it would be important to find a way for him to reveal the one thing on which he has thus far given scanty and unsatisfactory information, namely, diabetic acidosis. There is evidence that the dog stands ready as usual to do his part, and the fault has been with us. Von Noorden and Mohr have tried to make the matter too simple by affirming[2] that if a dog is kept a long time on bread diet so as to accustom him to carbohydrate like man and then changed suddenly to strict meat diet, a heavy ketonuria results. No experiments are cited in support of this assertion, which would seem to be imaginary; at any rate it is untrue, as we have found in a sufficient number of dogs, some of which had lived on carbohydrate for their entire lives. But Neubauer states the observation that very young dogs may show ketonuria on fasting, thus presenting an unusually close similarity to man. Veterinary literature proves that dogs are sus-

[2] Von Noorden, Die Zuckerkrankheit, 1912, p. 137.

ceptible not only to spontaneous diabetes but also to the termination in coma. Fasting phloridzinized dogs show heavy ketonuria, and von Mering, Lusk and others described the limp and semiconscious state which may result. Marriott demonstrated ketonemia in such animals, and we have found high ketonuria and low carbon dioxide in the terminal condition, which therefore seems truly analogous to diabetic coma. But as usual there are differences between phloridzin poisoning and diabetes. According to Baer a phloridzinized dog shows ketonuria only when there is a negative nitrogen balance. Perhaps this is why Geelmuyden found fat to diminish the ketonuria. None of our experiments have dealt with nitrogen balance sheets, but the impression certainly is that phloridzinized dogs show ketonuria on diets moderate in protein and high in fat, and this is strongly in accord with the probabilities. The most important distinction lies in the effect of carbohydrate and protein. Benedict and Osterberg proved that protein feeding causes a fall of 50 to 90 per cent. in the ketonuria even though the D : N ratios showed that all sugar formed from protein was quantitatively excreted. Obviously, protein does not work such a transformation in diabetic patients, and these authors correctly concluded that great caution must be used in interpreting the results of acidosis experiments in phloridzinized animals. The great majority of totally depancreatized dogs show only slight ketonuria and no coma or other acidosis symptoms. Sass using the Loewy-Zuntz titration method could detect no lowering of alkalinity in their blood. From the large number of depancreatized dogs in the Minkowski clinic Allard was able to report several dying in coma with considerable ketonuria. Kirk notes some similar deaths in his pancreas-fed dogs, also a higher ketonuria when fat was fed along with pancreas. Apparently the lower D : N ratio of the depancreatized dog suffices to explain the less marked acidosis as compared with the fasting phloridzinized dog, especially in view of the large quantities of protein katabolized. The great objection to totally depancreatized and Sandmeyer dogs is their cachexia and defective digestion.

Having dogs with severe diabetes and satisfactory digestive power, and desiring to produce in them if possible a facsimile of clinical acidosis, it is reasonable to proceed by subjecting them to the same conditions as human patients. To the question whether successful results can thus be obtained in dogs, the experiments now permit answering yes; that acidosis can be regularly produced in dogs not merely in one way but in three ways, of which gradations and combinations exist, but which are most conveniently described separately, in order to show the complete imitation of the human phenomena.

First we may take the classical treatment of severe diabetes. This has been based upon a too clever caloric conception. The

tendency of the diabetic is to emaciate because of deficient assimilation. The superficially smart idea has been to force up his weight by the trick of crowding calories into the diet to replace those lost in the urine, and of supplying these calories in the form of a food of which the body has only slight ability to relieve itself by excretion, namely, fat. The dog is an ideal subject for such a treatment. On the one hand, by reason of his lower D : N ratio, he loses less sugar than the very severe human cases, and he has a natural high resistance to acidosis; on the other hand, he is able to digest and metabolize far more food per kilogram of body weight than any human being. Therefore, it is an interesting experiment to take a suitable dog, free from cachexia, and see what happens when he is forced either to hold or to gain weight in the presence of severe diabetes. He cannot long hold weight on carbohydrate or protein; the one food for the purpose is fat. It is like the old fancy of the irresistible force meeting the immovable body; and in the present instance either digestion or metabolism, no matter how strong, must break down. Sometimes it is the former. In some dogs, and in any dog if the diet is not carefully adjusted, vomiting, diarrhea, and loss of weight prevent a perfect result. The tendency to digestive disturbances is like that of human patients on similar treatment. If digestion and absorption remain adequate, the breaking down of metabolism is manifested by increasing acidosis. There is repugnance to fat and hunger for carbohydrate as in human patients, but the animal's wishes must be disregarded, as has been done in human cases, and the fat given forcibly if necessary. The highest fat diet is the most quickly toxic, but excessive quantities of fat are not required, and both protein and carbohydrate aid digestion and do not interfere with the result so long as fat is continued. In the long run suet is probably the form of fat best liked and digested. Talcum powder is useful in the diet to control diarrhea. For the size of dogs used, the acidosis diet has sometimes been 150 to 200 grams suet and 200 to 400 grams beef-lung, or 100 to 150 grams suet, 200 grams lung, and 50 to 150 grams bread. Lipemia is present; there is malaise and depression of spirits as in patients with acidosis, and digestive upsets increase. If the animal is well suited for the purpose, if the diet is properly adjusted, and if there is enough day and night watching of all details, it can be shown that dogs thus go into fatal diabetic coma on full mixed diet. Dog 327 was our first and a very typical case. Table IV shows the clinical details of this final period.

Second, we may take the customary treatment of moderate diabetes and illustrate it in dogs. Suppose that suitable operation and overfeeding have produced a condition in which there is marked glycosuria on a kilogram of lung, but sugar-freedom on 800 grams lung, along with a fair state of nutrition and entire absence of

TABLE IV.—DOG 327 (PARTIALLY DEPANCREATIZED).

Date, 1916.	Blood.					Urine.							Weight,† kg.	Diet.	Remarks.
	Plasma sugar, %	Hb. %	CO_2, capacity.	Acetone, qual.	Lipemia, qual.	Volume, c.c.	Acetone, qual.	Total acetone,* mgm.	Total nitrogen, gm.	Ammonia nitrogen, gm.	N : NH_2-N, ratio.	Sugar, gm.			
April 15–16	..	..	..	..	..	922	++++++	91.3	9.082	1.259	7.22	57.33	..	200 gm. lung 200 gm. suet 50 gm. bread	Vomiting and diarrhea frequent during this period.
16–17	0.370	106	22.1	+	++++++	406	++++++	144.8	3.059	0.875	3.50	15.63	..	"	
17–18	0.400	108	29.0	++	++++++	530	+++++	129.9	6.201	0.737	8.40	30.81	19.0	"	
18–19	..	..	..	..	..	1186	+++++	134.0	10.081	1.257	8.00	66.22	18.4	"	Rapidly increasing acidosis symptoms.
19–20	0.400	..	18.5	+++	+++++++	1350	..	489.2	11.475	1.633	7.05	56.70	18.2	"	
20–21	0.314	..	23.3	..	+++++++	1480	..	389.2	10.952	1.717	6.36	51.80	..	"	
21–22	0.500	..	21.4	+++	+++++++	811	..	210.7	4.542	..	..	17.84	16.0	...	Coma.

* Total acetone bodies as acetone.

† Note precipitous fall.

ketonuria. Now place the dog on 600 to 800 grams lung and 100 to 200 grams suet, according to the classical method. There is no glycosuria, weight is gained, and the condition is splendid for weeks and possibly months. The treatment is highly successful. Closer examination shows the presence of hyperglycemia and slight ketonuria, which are usual in the patients of corresponding type. Glycosuria follows, illustrating the spontaneous downward progress which the authorities describe. This is cleared up by a few fast days on the Naunyn plan and the diet is again adjusted; it may now be 400 grams lung and 200 grams suet. The gain in weight continues as before, with hyperglycemia, ketonuria, and subsequent glycosuria. Again the fast days are used and the protein diminished, so that the diet is perhaps 200 grams lung and 200 grams suet. The same cycle is repeated. Now the dog is in splendid condition and spirits, the coat sleek, the appearance such that he might create a good impression out walking in the park, only he has difficulty in remaining sugar-free on even the protein minimum, and the fat may be pushed higher to maintain nutrition against the repeated fast days. If the dog has actually been kept fat, a fasting period about this time may diminish the glycosuria or it may remain high. The previously lively and hungry animal begins to show a curious little mournfulness and complete repugnance to food. A day or two later vomiting of clear mucus begins, and the dog drinks and vomits water. The acetone reaction is heavy; the ferric chloride may be heavy or slight. The alkali reserve of the blood falls low, and the complete picture of patients who go into fatal acidosis on fasting is reproduced. Dogs of the type first described are also subject to this result of fasting if they have been kept fat enough, but fattening is easiest in absence of glycosuria. As in human patients this form of acidosis more resembles the collapse or heart-failure type of Frerichs. The respiration is less typical and consciousness may be retained practically to the end. The outstanding features are the nausea and vomiting and the profound collapse of strength. Table II represents the terminal stage of this condition in dog 280.

Incidentally it may be noted that the cachexia which sometimes causes an apparent suppression of sugar formation in fasting depancreatized dogs is absent in these severely diabetic, partially depancreatized animals, so that their glycosuria and hyperglycemia typically persist almost or quite to the time of death.

The third type of acidosis in dogs is exemplified by diabetic animals kept free from glycosuria by regulated diet or by those in which the amount of pancreatic tissue removed is not quite sufficient to give rise to diabetes. They are free from acidosis on protein diet or on fasting, but on a carbohydrate-free diet high in fat they sooner or later develop marked ketonuria. The protein ration may be governed by the capacity of the stomach. Prob-

ably high protein tends to increase susceptibility to diabetic glycosuria and diminish the tendency to ketonuria. These experiments also may extend over weeks or months, but we have proved upon many dogs that with enough fat in the diet the result is invariable. The qualitative acetone test is heavy but the quantitative output relatively small, generally below 1 gram. An example of this condition is given incidentally in the record of dog 356 (Table V), with potentially severe diabetes. Partially depancreatized non-diabetic dogs on a diet of 150 to 300 grams suet and perhaps an equal amount of lung may thrive in spite of ketonuria for a longer or shorter time. Ketonuria is apt to be slight. But the final outcome appears in one of two forms. One may be digestive failure and consequent loss of weight and strength, with cessation of ketonuria. In the other form the routine measures against vomiting and diarrhea may succeed, but the end comes with a remarkable spastic and ataxic condition, with terminal weakness, convulsions and death. The absence of ketonuria in adult normal dogs on fasting has been confirmed, and has been found true also on high fat diet extending over several months and still continuing. Tests on puppies are only beginning. One young collie suddenly showed a heavy acetone reaction after two weeks of fasting. High fat diet was immediately given. On the third day of this the dog, which was not known to have been pregnant, aborted. This was some two weeks ago. The acetone reaction with low quantitative values has not ceased, but the dog continues to act well. It is not known whether this idiosyncrasy is present because the dog is young, or because of the collie breed, or because of the pregnancy. Normal controls flourish indefinitely, without ketonuria or with only traces, on the same fat-protein diet which causes acidosis in partially depancreatized dogs. A certain number of normal dogs with a sufficient preponderance of fat over protein in the diet develop ataxia and fatal intoxication seemingly identical with that of partially depancreatized dogs, but ketonuria is generally absent or slight. Digestion is upset in them as in the partially depancreatized animals; accordingly, ketonuria cannot be attributed to fatty indigestion. This state of intoxication will require subsequent mention. In partially depancreatized animals the sugar tolerance is diminished. If the ketonuria be interpreted as a diminished fat tolerance, it affords no evidence concerning the unity or plurality of the pancreatic secretion, and in absence of evidence the presumption remains in favor of the former. These experiments are mainly useful as showing that a species which normally has a high resistance to acidosis is made readily susceptible by partial pancreatectomy, and as thus furnishing conclusive proof that the simple balance between fats and other foods does not alone govern ketogenesis but that a specific internal function of the pancreas is at least one of the factors concerned.

TABLE V.—DOG 356 (PARTIALLY DEPANCREATIZED).

Date, 1916.	Blood.						Urine.‡								Weight in kg.	Diet.
	Plasma sugar, %	Hb., %	CO_2 capacity.	Acetone, qual.	Total acetone,* mgm. per 100 c.c.	Lipemia, qual.	Volume, c.c.	Reaction.	Acetone, qual.	Total acetone,† mgm.	Sugar, gm.	Total nitrogen, gm.	Ammonia nitrogen, gm.	N : NH_3-N, ratio.		
Aug.																
24–25	0.200	..	..	..	..	..	269	..	+	..	2.60	7.500	0.820	9.15	11.1	400 gm. suet.
25–26	0.124	106	..	..	..	..	160	..	0	..	+	4.110	0.510	8.07	..	300 gm. suet.
26–27	0.111	..	..	..	..	..	246	..	0	..	0	2.100	1.560	1.35	..	200 gm. suet.
27–28	0.099	..	53.8	..	..	..	192	..	0	..	0	2.670	1.130	2.36	11.4	100 gm. lung; 200 gm. suet.
28–29	..	..	..	..	..	..	352	..	0	..	0	4.100	1.640	2.50	..	Fasting.
29–30	..	..	..	..	..	..	382	..	0	113.1	0	3.570	2.100	1.70	..	100 gm. lung; 100 gm. suet.
30–31	..	..	..	..	..	..	172	..	+	..	0	2.510	1.360	1.84	..	100 gm. lung; 200 gm. suet.
31– 1	..	..	..	..	..	..	140	..	0	..	0	1.580	0.782	2.02	11.4	150 gm. lung; 150 gm. suet.
Sept.																
1– 2	..	..	..	..	..	..	176	..	+	..	0	2.410	0.950	2.54	..	150 gm. lung; 250 gm. suet.
2– 3	..	..	..	..	..	..	160	..	0	..	0	4.320	1.320	3.28	..	150 gm. lung; 250 gm. suet.
3– 4	..	..	..	..	..	..	116	..	+	..	0	1.540	1.020	1.51	..	150 gm. suet.
4– 5	..	..	..	..	..	..	295	..	+	64.9	0	1.593	1.180	1.32	11.75	100 gm. lung; 200 gm. suet.
5– 6	..	..	..	..	..	..	140†	..	++	22.4	0	0.975	0.364	2.66		
6– 7	0.095	90	48.5	0	..	0	357	..	+	86.0	0	3.642	1.175	3.08	11.80	Ditto.
7– 8	..	..	..	..	..	..	258	..	+	49.0	0	2.296	0.413	5.55	..	Ditto.
8– 9	0.083	..	57.9	0	..	0	260	..	+	44.2	0	..	1.000	..	..	Ditto; 8 gm. sod. bicarb.
9–10	..	..	..	..	..	..	842	Alkaline	..	101.0	0	6.399	1.263	5.07	..	Ditto; 5 gm. sod. bicarb.
10–11	0.093	86	67.3	0	..	0	378	Alkaline	0	49.1	0	5.640	0.491	11.50	11.81	Ditto; 10 gm. sod. bicarb.
11–12	..	..	..	..	..	..	380	Alkaline	0	38.0	0	1.642	0.144	11.40	..	Ditto.
12–13	..	..	..	..	..	..	904	Neutral	..	99.5	0	0.814	0.181	4.50	..	Ditto; vomited.
13–14	..	..	..	..	..	..	342	Alkaline	+	68.5	0	2.743	1.180	2.32	..	Ditto.
14–15	0.115	105	67.2	?	..	+++++	170	Alkaline	++++	64.8	0	1.578	0.876	1.80	..	Ditto.
15–16	0.121	93	60.5	+	..	++++	360	Alkaline	++++	84.0	0	3.384	1.332	2.56	..	Ditto.
16–17	0.123	..	58.6	..	..	+	438	Alkaline	++++	53.6	0	3.503	1.051	3.34	..	Ditto.
17–18	0.121	96	64.3	0	..	+	412	Acid	..	30.8	0	0.676	0.144	4.68	12.05	Ditto.
18–19	0.128	..	51.9	0	..	+	220	Alkaline	++++	41.8	0	1.786	0.759	2.36	..	Ditto.
19–20	..	..	..	..	..	..	418	Alkaline	++++	79.7	0	5.643	1.672	3.37	..	Ditto.
20–21	0.149	105	..	+	25.5	+++	664	Alkaline	++++	117.4	0	2.523	1.195	2.10	..	Ditto.
21–22	..	..	..	..	..	..	768	Alkaline	+++++	93.7	0	2.611	1.459	1.79	..	Ditto; vomited.
22–23	..	..	..	..	..	..	670	Acid	..	34.4	0	1.983	0.670	2.95	..	Ditto.
23–24	..	..	..	..	..	..	344	Neutral	..	60.0	0	1.238	0.241	5.12	..	Ditto.
24–25	..	..	..	..	..	..	600	Alkaline	++	..	0	3.108	1.440	2.16	..	Ditto.
25–26	0.179	108	59.5	+++	30.5	++++	870	Acid	++++	..	0	2.302	1.657	1.40	12.20	Ditto.
26–27	..	..	..	..	..	..	790	Alkaline	..	213.3	0	2.465	1.422	1.74	..	Ditto.
27–28	..	98	63.3	0	18.9	+	733	Alkaline	..	43.9	0	1.833	1.393	1.32	..	Ditto.
28–29	0.322	86	61.4	+	..	0	400	Alkaline	..	20.8	0	2.080	0.780	2.66	..	200 gm. lung.
29–30	0.400	..	..	0	31.2	0	565	Alkaline	..	26.2	0	5.763	1.441	4.00	..	
30– 1	0.435	89	..	..	35.7	..	550	Alkaline	+	25.3	5.65	4.554	1.953	2.33	..	
Oct.																
1– 2	0.250	92	61.4	0	23.2	0	468	Alkaline	+	..	0	2.621	0.772	3.40	..	
2– 3	0.192	95	59.5	0	..	0	636	Alkaline	0	..	0	2.582	0.670	3.85	..	
3– 4	0.175	88	59.5	0	..	0	605	Alkaline	0	..	0	2.009	0.484	4.14	..	Fasting.
4– 5	0.208	82	59.5	0	..	0	828	Alkaline	0	..	0	2.385	0.621	3.84	..	
5– 6	0.235	88	63.3	+	..	0	842	Acid	0	..	0	2.055	0.505	4.07	..	
6– 7	0.169	76	..	0	..	0	870	..	0	..	0	2.242	0.686	3.25	..	
7– 8	..	..	..	..	..	..	600	Alkaline	0	..	0	..	0.420	..	..	
Nov.																
3– 4	0.200	..	..	..	..	..	..	..	..	..	..	..	..	..	8.15	200 gm. lung.

‡ Not catheterized. * Total acetone bodies as acetone. † Incomplete specimen.

Of various points perhaps deserving mention, six features of canine acidosis will be chosen for separate consideration. First there are some peculiarities of species seen in the clinical picture. A characteristic of human coma is that the cerebral centers are anesthetized while the respiratory center is stimulated. It may be taken as a general rule that dogs lose consciousness less readily than men, and this applies to their diabetic coma. They begin by showing weakness, drunken gait, and dyspnea especially on slight exertion. The symptoms increase until the animal cannot stand, and the Kussmaul breathing may be typical. The corneal reflex is practically never lost, and even attention to surroundings may be preserved almost to the last. It might appear that the motor centers are selectively intoxicated, until observation shows there is apparent absence of pain in the exposure of bloodvessels or other operations, so that the sensory depression is fully equal to that in human coma, in which a knife-cut frequently provokes some response. The low blood-pressure emphasized by Ehrmann and the soft eyeball noted by Riesman and others have not been tested. Diarrhea sometimes occurs with human coma; in dogs it is invariably present and tinged with dark blood. It occurs whether the coma is produced by feeding or fasting, by diabetes or by phloridzin. It is therefore of metabolic not of digestive origin. At autopsy the liver is typically large and fatty and much fat may be present in the body. There is more or less venous engorgement of the intestine and other viscera, which is the only apparent explanation of the bloody diarrhea, though the bowel contents begin to appear bloody only toward the rectum.

Second, there is the obvious question of the influence of reaction. Toward the end the carbon dioxide capacity of the plasma falls as in human cases, and to a quite similar level. But one advantage of studying the same phenomenon in various species is seen in the fact that in the dog it is easy to maintain normal or supernormal alkalinity of the blood from start to finish, or to raise it suddenly toward the end when it has fallen. In man this is difficult to accomplish even by the highest alkali dosage, but some clinicians have asserted that continuous alkalinity of the urine has failed to save their patients. A few personal observations, and my conception of the acidosis process, have convinced me that this view is essentially correct. Probably the typical dyspnea and coma never occur in man or dog except with acid intoxication. Probably the upholders of the acid intoxication theory of coma are correct on this point, which is, after all, their main contention. Where they seem to be clearly wrong is in the more important matter of extending this idea to mean that a maintenance of reaction would prevent intoxication. Conceivably the secret of the improvement sometimes produced by bicarbonate may lie in an unloading of toxic substances from the cells rather than in a shift-

ing of the alkali-acid equilibrium *per se*. Aside from a possible, very brief, rise in blood-pressure, sodium bicarbonate intravenously or otherwise brings no visible benefit to a dog dying of acidosis. Keeping the alkaline reserve of the plasma continuously normal by means of it or any form or combination of alkaline salts apparently does not prolong the life of a diabetic dog by a single day. The experiments support the conception that acidosis and coma essentially represent an intoxication due to a specific breakdown in metabolism, and that the tendency to alteration of reaction is only an incidental phenomenon.

A third point, closely connected with this, is the ammonia excretion. This was considered the most reliable index of acidosis until the introduction of the tests of alveolar air and blood. Researches beginning with Walter have established that different species vary in their ability to protect themselves against acid intoxication by ammonia formation, and that the quantity of ammonia that can be produced is partly governed by the amount of protein in the diet. Owing particularly to the work of Magnus-Levy and his masterly reviews of the literature, the prevalent tendency is to see in the ammonia solely a reaction to acid poisoning. Therefore, it is well to read the excellent review by Ewing, which gives fairer consideration to other factors possibly concerned. Since the early work of Minkowski, Schütz and others it has seemed that the liver function is one governing factor, and Allard, Rolly and others have upheld the importance of this element in diabetic acidosis. The dog experiments promise to contribute information on this point, but they do not yet permit a conclusion. Normal dogs seem regularly to show low ammonia notwithstanding high fat diet. One of our supposedly normal dogs injured its back while out for exercise, with resultant transitory paraplegia and subsequent polyuria. This dog thrives on either carbohydrate or fat, but shows low ammonia on the former and high ammonia on the latter. Partially depancreatized dogs react to fat diet with such a vigorous ammonia production that the urine is sometimes turned alkaline. Dog 356 (Table V) here gives one example. Alkaline urine on protein-fat diet makes any experienced investigator think of cystitis. To exclude this we now for the most part omit all catheterization and test the animals with a change of food or with alkali. When carbohydrate diet or, as with dog 356, sodium bicarbonate causes a prompt fall in the ammonia and rise in the $N : NH_3$ ratio, cystitis is considered improbable. It is not certain that alkali must necessarily reduce ammonia excretion to normal. The ammonia relations shown in dog 356 and others would seem indicative of reaction or overreaction to acid. Over against these are the relatively low ammonia figures and high ratios in dog 327 (Table IV), notwithstanding the falling alkalinity of the blood and impending death in coma. The essential known difference between the animals is that dog 327

constantly had carbohydrate in the diet. It is possible that the exceptional results are accidental, and as yet we lack the necessary series of experiments to say that they are significant.

The acetone bodies represent a fourth point requiring brief notice. In general, dogs excrete less of them per kilogram of body weight than human patients. It must be remembered that the excretion by human patients is generally not very high except under the influence of alkali therapy, and coma is possible with low ketonuria. The ketonemia seems to be on a par with that of human patients. It is as if the dog's kidney were relatively impermeable to acetone bodies. Also, sodium bicarbonate seems inefficient to sweep them out. A further distinction is that acetone represents a higher proportion of the total acetone bodies than in severe human cases. There is greater similarity to the milder human cases in this regard. What significance it may have in connection with the natural difference between dog and man respecting acidosis is unknown. Miss Wishart conceived the idea of applying the Rothera acetone test to the blood plasma. The test has proved very useful as a routine in the animal work. It has also given dependable results when applied to human patients here and in Dr. Joslin's clinic in Boston. The significant color range varies from the faintest tinge up to the deepest permanganate color. The proteins or other substances in plasma seem to cause no interference. The reaction appears unsuited for exact quantitative application, but it gives a quick, rough idea whether there is dangerous ketonemia or not and whether a quantitative determination is worth while; and as its results do not always run parallel to the urinary reactions it would seem that qualitative tests are more valuable in the plasma than in the urine. The suggestion of Embden and others that acetone is formed chiefly in the urine during or after excretion, from diacetic acid which is the actual circulating substance, appears to be contradicted by the strong acetone and weaker diacetic tests obtained in the plasma. Specific poisoning with acetone bodies has been the principal hypothesis opposed to the acid intoxication theory of acidosis. In denying the latter view we are not necessarily thrown back upon the former. The cause of damage from the metabolic breakdown may or may not be subject to chemical analysis by present known methods. The present work adds to the means for approaching the problem. It is possible that the acetone bodies may some day prove to be an index rather than the cause of the intoxication in acidosis.

A fifth point for mention is the behavior of the kidney, which has recently been studied in human diabetics by McLean and more particularly by Fitz, but which time has not permitted investigating in our animals. Incidental observations show that the usual polyuria of severely diabetic animals is generally diminished

on high fat diet, and oliguria is frequent in spite of high sugar percentages in blood and urine. For some reason thirst is lacking, so the change is not altogether renal. The kidneys are sometimes remarkably impermeable to sugar, after sugar feeding in mild cases but more notably after fat feeding in severe cases, when it is possible to have 0.4 per cent. blood-sugar without glycosuria. An example is furnished by the record of dog 356 (Table V). Neither water nor sodium bicarbonate has been observed to cause edema, but the latter seems not to produce such thirst and diuresis in acidosis animals as in normal ones, and perhaps this is why acetone bodies are not swept out as in the human. Albuminuria is common in acidosis and in simple fat intoxication, but the few observations made have not shown casts. The kidneys of dogs with advanced acidosis have always shown gross and microscopic alterations as far as yet examined, the Armanni vacuolation of certain tubule cells being the most constant. Glycogenic degeneration described by Ehrlich has not been demonstrable by Best's carmine stain. From the absence of edema after nephrectomy and other known facts it is doubtful if dogs are suited for accurate imitation of the renal peculiarities of human diabetics, but it seems probable that excessive fat ingestion has directly or indirectly an injurious effect on the kidneys in both patients and dogs, and that this feature is worthy of more study than we have been able to give it.

The sixth and last point for special mention is the general position of fat in the dietary. The early investigations of the total metabolism founded the conception of the caloric requirement and isodynamic equivalents. A protein minimum has been partially worked out. It has been proved that carbohydrate has a slightly greater sparing action than fat, and particularly by Mendel has been established the importance of individual amino acids for nutrition and growth. The need of salts is known, and the so-called vitamines are a recent discovery. This practically sums up the existing knowledge of nutrition. Against the prevalent belief that a starving organism is benefited by whatever food it can obtain, should be raised the question whether this is ever true of any non-protein food taken in quantities approaching the total caloric requirement each day. The question pertains to the benign carbohydrate. Concerning fat there is no question. Fat unbalanced by adequate quantities of other foods is a poison. It should be recalled that carnivorous animals subsist largely on protein, and though the Eskimo consumes much fat, he also, according to the Krogh report, eats several kilograms of lean meat daily. After a few days of pure fat diet the most voracious cur will starve to death before he will touch it further, and the more strictly carnivorous cat is still less tolerant of fat-rich diet. Against forced feeding the organism protects itself by vomiting, diarrhea, and remarkable cessation of absorption. No form of emulsification or admixture

TABLE VI.—DOG 394 (PARTIALLY DEPANCREATIZED).

Date, 1916.	Blood.‡					Urine.§							Weight, kg.	Diet.	Remarks.
	Plasma sugar, %	Hb., %	CO_2 capacity.	Total acetone,* mgm. per 100 c.c.	Total fat, plasma, %	Volume, c.c.	Total acetone,* mgm.	Sugar, gm.	Total nitrogen, gm.	Ammonia nitrogen, gm.	N : NH_3-N ratio.	D : N ratio.			
Aug.															
6–7	..	..	..	..	..	1731	360.0	48.5	..	..	..	..	..		
7–8	0.285	82	47.1	83.2	..	1302	248.0	43.4	..	..	..	..	..	100 gm. lung; 100 gm. suet;	
8–9	0.270	..	51.0	94.5	0.566	1178	..	60.8	5.30	..	..	..	10.1	100 gm. bread	
9–10	0.250	106	51.0	36.4	..	1900	416.0	80.0	7.40	..	..	..	..		
10–11	0.232	92	..	18.5	0.566	800	130.5	52.0	4.71	0.44	10.71	..	..		
11–12	0.204	..	..	44.8	0.583	630	134.9	23.3	9.50	0.85	11.18	2.45	..		
12–13	..	..	..	..	..	3080†	591.0	19.1	8.65	1.23	7.04	2.21	..	400 gm. lung, 100 gm. suet.	
13–14	0.286	103	32.8	50.1	..	1605	596.0	32.1	11.40	1.61	7.08	2.82	..		
14–15	0.364	95	40.4	23.4	0.490	704	182.4	22.8	9.10	0.91	10.00	2.50	10.0		
15–16	0.250	95	31.9	80.4	0.290	646	124.8	19.4	8.30	0.84	9.88	2.34	..		
16–17	0.377	95	31.9	..	2.380	1030	224.9	35.2	9.27	1.40	6.63	..	9.77		
17–18	0.322	..	51.9	41.0	..	1800	195.1	72.0	10.80	1.62	6.68	..	9.70	400 gm. lung; 100 gm. suet;	
18–19	0.365	90	38.5	30.6	1.840	820	288.0	41.0	9.50	0.82	11.58	..	9.80	100 gm. bread	Dark diarrhea.
19–20	..	..	..	..	..	2350†	742.1	47.0	10.10	1.22	8.30	..	..		
20–21	0.276	..	30.9	73.2	0.430	662	119.6	49.2	8.15	0.76	10.72	..	9.76		
21–22	0.263	51	..	41.1	0.765	406	116.7	13.2	..	0.67	..	..	9.50		
22–23	0.295	35	32.8	39.8	0.591	515	226.5	19.5	7.70	0.77	10.00	2.53	9.50		Unwell; entire diet forced.
23–24	..	..	..	..	..	584	163.8	10.7	5.95	0.73	8.15	1.80	9.07		Eats all diet promptly.
24–25	0.214	39	34.7	36.9	0.825	820	316.8	28.7	8.60	0.90	9.55	3.34	9.30	400 gm. lung; 200 gm. suet.	Seriously ill; fed forcibly.
25–26	0.314	26	40.9	29.2	1.090	686	332.2	15.6	6.65	0.82	8.12	2.35	9.16		
26–27	0.237	..	48.1	..	..	680	214.5	14.3	9.85	0.88	11.15	1.45	..		5 gm. sodium bicarbonate.
27–28	0.256	25	60.5	60.3	0.785	390	170.0	7.2	6.00	1.88△	3.19	1.20	8.75		
28–29	0.354	22	54.8	26.2	0.895	675	230.9	14.1	6.75	1.59△	4.25	2.09	8.51	Not fed	Good condition and spirits.

‡ Blood drawn twenty-four hours after feeding. § Catheterized to separate diet periods. * Total acetone bodies as acetone. † Water spilled. △ Cystitis?

with talcum or other inert substances to give consistency resembling that of the normal ration avails against this toxic action. The small proportion of protein contained in cream or suet gives only partial protection. The same result follows more slowly whenever the proportion of fat to protein or carbohydrate in the diet is too high. The craving of diabetic patients for carbohydrate is often illustrated in such dogs. It should be worth while to determine a law of balance for normal animals. Not only has the diabetic animal a specific sensitiveness to fat, but on low protein ration it must be unable to bear as much fat as an animal on high protein. If the danger of glycosuria prevents increasing the protein, intoxication can be avoided by diminishing the fat. The animal is thinner but safer, hungry instead of nauseated. Diabetic patients have been treated on protein requirement and caloric computations and on general experience of what they will endure. One feature of this experience is that the great majority of severely diabetic patients acquire a repugnance to the prescribed diet and refuse to endure it. By will-power they sometimes endure it for a time. Raulston and Woodyatt's patient adhered for nearly three weeks to a diet of three eggs and 800 c.c. of 16 per cent. cream daily. They employed this as a temporary measure, but such low protein, full calory diets have been the ideal of the best workers under the Naunyn method. The fact is that such a diet will send a diabetic dog into coma, and it is questionable how long normal dogs could tolerate it. It thus appears that patients were right in much of their conduct, and their stealing of carbohydrate was not entirely due to original sin but was rather prompted by physiological necessity. They live in fair comfort on moderate protein and little or no carbohydrate as long as the fat is kept suitably low. They behave much more rationally toward simple hunger for all classes of foods than they did toward the former excessive craving for carbohydrate. Lack of self-control still claims many victims, but the proportion of patients willing to follow diet faithfully has been increased by reason of the more natural balance of foods in the diet.

III. Influence on Carbohydrate Utilization.

The third phase of the role of fat in diabetes to be considered now is its influence on carbohydrate utilization, on hyperglycemia and glycosuria.

The literature on this subject is scanty. A small number of writers believe it probable that sugar is formed from fat. A somewhat greater number, including Magnus-Levy, admit the possibility. The great majority recognize the occurrence of such a process in plants, but find no evidence of it in animals. Attempts have been made to demonstrate it in animal experiments, but these have failed so completely that they are not worth reviewing;

whereas, on the other hand, the non-increase of sugar after fat feeding, the dextrose-nitrogen ratio, and the respiratory quotient, as found by Lusk and others, offer seemingly conclusive proof of the absence of such a transformation in the intense sugar-hunger of phloridzin-poisoning. Although Donkin insisted on skim milk for his milk cure, and that cream spoiled it, the first to assert that fat increases diabetic glycosuria was Lichtheim, whose perfectly correct statement is mentioned with disapproval by Weintraud. Weintraud argued that even if fat should in certain cases cause the excretion of a few grams of extra sugar, the food value of the fat is far greater than this, so there is clear benefit. This has remained the position of the Naunyn school. Lenné, von Noorden and others, who hold extreme views of conversion of fat into sugar, nevertheless use fat to make up a full caloric ration. Von Noorden confesses to prescribing fat perhaps more liberally than anybody else. He and Falta and other pupils mention occasional so-called "fat-sensitive" patients whose glycosuria is increased by fat feeding; but this effect is said to follow only the overnutrition produced by excessive fat ingestion, and fat in the quantities practically employed is held not to increase glycosuria, because if it were withheld its place in metabolism would supposedly be filled by body-fat. I have reviewed elsewhere reports of dextrose-nitrogen ratios supposedly proving sugar formation from fat in diabetic patients, but actually proving they were not adequately watched; also the other observations from Griesinger down to Benedict and Joslin and Du Bois demonstrating that no higher dextrose-nitrogen ratios than Lusk's 3.65 value are found in even the severest clinical diabetes, and the respiratory quotients further assure the non-formation of sugar from fat. In view of the general acceptance of these facts it is natural that the possibility of increase of glycosuria from fat feeding should be generally ignored. If an occasional voice asserts from time to time that fat increases glycosuria, the protest is directed only against fat rations considered excessive, and only the most slight and transitory undernutrition has been countenanced by such authors.

It is likewise natural that the glycosuria attributed to fat should be small and that the so-called sensitiveness should be apparent in relatively few cases. The effect of fat was above characterized as insidious and cumulative, even with respect to the acetone bodies which are formed from fat; and at least an equally occult influence should be anticipated with respect to sugar, which seemingly is not formed directly from the fat itself. Its action, though not absent in mild cases, is necessarily difficult to demonstrate. The heavy and variable glycosuria of average severe cases and the already maximal output in the extreme cases hopelessly mask the effect of fat, which therefore is only demonstrable rather doubtfully in an intermediate group. Once more the severe cases freed from glyco-

suria and acidosis afford the best clinical experimental material. Dr. Fitz has been performing some experiments of this type, with unusually complete laboratory observations. One of his protocols is here reproduced (Table VII). The patient, who developed diabetes at the age of fifteen, is now nineteen, and has been under treatment at the Institute for two years. She represents one of the cases in which tolerance is built up very slowly and with difficulty, and on account of tenement environment she loses in a few weeks at home as much as is gained in months at the hospital. Her general condition and power of assimilation are therefore known by long experience. The record begins with high blood-sugar produced by a slightly excessive previous diet. The diet throughout contained a fixed quantity of thrice-boiled vegetables, but no other possible source of carbohydrate. The procedure consisted in keeping the protein intake constant and increasing the fat by about 5 grams daily. The peculiarities concerning chlorides and other features will be discussed by Dr. Fitz elsewhere. The ketone and ammonia excretion increased moderately. The blood sugar first fell, then rose, as the fat was increased. The patient felt better on the higher fat. Such well-being is transitory. Glycosuria appeared in traces and increased to 21 grams. High glycosuria and acidosis can be produced by continuing such an experiment, but safety required checking the injury here by a fast day. It is feasible in selected cases to show that the symptoms subside on simple omission or reduction of fat. This patient is an example of those who can demonstrably live in fair comfort and nutrition for at least several years on low diet almost or absolutely free from carbohydrate, but who would die rather promptly if the traditional building-up process with fat were attempted.

The earliest experiments showing the benefits of continued reduced nutritional level in diabetes were performed on dogs. Notwithstanding the evident clinical results in severe cases there remain physicians who, conceding that such methods may be useful for such cases, find in their experience that patients feel best on liberal nutrition, and see no harm in allowing plenty of fat in the cases in which no immediate injury is perceptible. Also, there are other clinicians who hold that alleged radical differences between diabetic patients prevent drawing general conclusions or treating according to a unified broad conception, and who emphasize spontaneous fluctuations due to infections or other causes, and who try to draw distinctions between the properties of various kinds of fats, and who maintain the comfortable interpretation that bad results under their methods are due to a progressive downward tendency inherent in the condition itself. By choosing the severest cases obtainable and including the poor and ignorant we have made a high death-rate inevitable. Furthermore, our own management has not been perfect, and we have sometimes given too

TABLE VII.—PATIENT B. D. P.†

Date, 1916.	Blood.					Urine.							Weight, kg.	Diet.△			
	Urea nitrogen, mgm. per 100 c.c.	Plasma acetone,* mgm. per 100 c.c.	Plasma chloride, %	Sugar, %	Plasma, CO_2 capacity	Volume, c.c.	Total nitrogen, gm.‡	Ammonia nitrogen, gm.	N : NH_2-N ratio.	Acetone,* gm.	Chloride, gm.	Sugar, gm.		Protein, gm.	Fat, gm.	Calories.	NaCl, gm.
Sept. 29–30	..	25	0.594	0.204	63.0	4150	4.31	0.54	7.96	1.67	12.85	Trace	37.8	7.4	13.5	150	10
30– 1	..	..	..	..	..	3235	7.14	0.94	7.60	2.56	6.95	Neg.	36.4	33.0	34.0	450	10
Oct. 1– 2	..	..	..	..	..	3380	8.00	0.98	8.16	2.72	3.89	"	36.1	40.0	47.0	605	10
2– 3	..	33	0.606	0.172	65.4	3560	8.00	1.00	8.00	2.43	8.20	"	36.1	40.0	52.0	650	10
3– 4	..	..	..	..	..	3765	9.08	0.94	9.65	1.85	10.00	"	36.1	40.0	57.5	700	10
4– 5	6.9	25	0.593	0.143	66.3	3970	8.65	0.95	9.10	2.01	13.30	"	36.1	40.0	63.5	750	10
5– 6	..	..	..	..	..	3995	7.75	1.00	7.75	2.62	11.80	"	36.0	40.0	68.5	800	10
6– 7	..	24	0.588	0.192	67.4	3360	8.30	1.44	5.76	..	11.30	..	35.6	40.0	73.5	850	10
7– 8	..	..	..	..	..	3595	9.67	0.93	10.40	2.24	7.74	"	35.9	40.0	80.0	900	10
8– 9	..	..	..	..	..	3745	10.70	1.05	10.20	1.63	11.60	"	35.8	40.0	85.1	955	10
9–10	7.0	26	..	0.204	63.0	3555	9.70	0.89	10.90	1.48	11.90	"	35.9	40.0	90.0	1000	10
10–11	..	..	..	..	..	3835	10.25	0.84	12.20	0.96	12.45	"	35.8	40.0	95.0	1050	10
11–12	..	24	0.582	0.182	68.8	3530	8.26	0.84	9.85	1.35	11.12	"	35.5	40.0	100.0	1100	10
12–13	..	..	..	..	..	3290	9.71	0.95	10.21	1.64	9.37	Traces	35.6	40.0	105.0	1150	10
13–14	..	25	0.581	0.200	65.9	3270	7.64	1.18	6.50	2.50	8.82	"	35.5	40.0	110.0	1200	10
14–15	..	..	..	..	..	3465	10.60	1.18	9.00	3.46	10.39	"	35.6	40.0	115.0	1250	10
15–16	..	28	0.588	0.176	61.2	3120	12.25	1.34	9.15	4.40	8.26	1.85	35.4	40.0	120.0	1300	10
16–17	9.9	..	..	..	..	3140	12.20	1.48	8.25	2.86	10.98	21.32	35.6	40.0	120.0	1300	10
17–18	..	..	..	..	..	3330	10.20	1.63	6.25	4.16	8.66	13.32	35.7	40.0	120.0	1300	10
18	8.4	30	0.587	0.221	59.8	..	..	..	..	..	..	..	..	..	Fasting		

† Entire experiment by Dr. Fitz. * Total acetone bodies as acetone. ‡ Note increased nitrogen output as fat is increased.
△ 300 gm. thrice-boiled vegetables daily not reckoned; also 300 c.c. soup daily, containing 1.5 gm. N., not included in the protein figures.

high diets and committed other mistakes. This record might be pointed to in support of the allegation that while fasting is good for coma, and has in fact been employed by others previously, the end result is the same anyhow, and in deciding between coma and starvation it is better to choose the former and keep the patients as comfortable as possible. In defense we might point to the very high proportion of these patients apparently saved and improving and enjoying even comfort and usefulness in cases and to an extent apparently impossible under any former methods. Certainly the experience of the great majority of specialists and general practitioners has declared favorably for the benefits of the new plan, and it would not be possible for a treatment to receive a more cordial reception by the medical profession. But both the permanent establishment of the practical treatment on a basis not shaken by every wind of doctrine, and the full determination of the theoretical and scientific significance of the changes thus produced in the diabetic condition, require a clear demonstration of the principles at issue in animal experiments, in which all extraneous and accidental factors can be excluded, and facts concerning the role of fat in relation to diabetic glycosuria and carbohydrate metabolism can be proved by methods beyond the scope of the personal equation.

The first step in such an investigation is to define the potentialities of the experimental material. The material consists of dogs or other animals with injury of assimilation produced by a surgical resection. They are seemingly free from variations due to heredity or the innate tendencies ascribed to human patients. Their special peculiarities and possibilities must be learned. Glycosuria is more liable to cease spontaneously in cats than in dogs, apparently owing to a slower tendency to degeneration and a greater power of recovery in their exhausted islets. Thiroloix and Jacob first announced that mildly diabetic dogs may be sent into the severe fatal form by carbohydrate overfeeding, like human patients, but they gave no description of controls, and their observations were apparently not long enough to reveal the final fate of the dogs not fed on carbohydrate. On first coming to the Rockefeller Institute over three years ago, I set apart some of the first dogs for prolonged experiments covering this point. Some were to be subjected to successive removal of small pancreatic fragments for microscopic and other purposes. Others after one initial operation were merely kept on certain diets. Shorter tests under a year in length were performed on other dogs and other species. No animals succumbed to operation, but a number to the environment. The finished series is not as perfect as planned, but is adequate for decisive results. The proportion of the pancreas which must be removed to produce a given grade of diabetes is fairly constant in a given species, though the rare individual exceptions

are sometimes marked. There are great differences between species, which are independent of the natural sugar tolerance, diet, pancreatic structure, or any other known factors. The general tendency of the pancreas is to hypertrophy after partial ablation, most markedly in young animals, as Homans stated. Extirpation to any point short of producing diabetes causes no tendency to degeneration of the remnant or to downward progress clinically. When the operation is sufficient for mild diabetes, the food tolerance as ascertained after allowing a few weeks for recovery from trauma will generally hold good for a number of months on suitable diet. There is a tendency to some gain in tolerance, but this is usually easy to break down. It is hard to distinguish the true from a false gain in tolerance, characterized by hyperglycemia without glycosuria. Previous authors have reported this phenomenon after repetitions of adrenalin and in old human diabetes. It is present at a certain stage of overfeeding with sugar, protein, or fat. Part of it may represent renal damage, but a part is probably some reaction connected with the basic nature of diabetes. Within proper limits the animals are very valuable for testing the effects of all sorts of agencies upon the carbohydrate and other assimilation and for distinguishing between diabetes and accidental glycosuria. The downward progress conclusively shown by feeding beyond the tolerance with carbohydrate or protein has been previously outlined. The experiments of feeding within the apparent tolerance have been only recently coming to completion. Dogs with a limited carbohydrate tolerance, when kept long enough at normal weight with carbohydrate below the limit, or on lean meat only, or on mixed lean and fat, finally show a gradual fall in tolerance, and all but one of the animals of this series have died of diabetes. The remaining one, now on protein-fat ration, not only has lost all carbohydrate tolerance but shows active diabetes in the form of constant hyperglycemia and ketonuria. There is no reason why diabetes in an Eskimo should not begin in this way, but the ordinary human diet is such that glycosuria precedes ketonuria. The sudden or slow onset of human diabetes can be imitated in dogs. Several interesting examples of apparent onset after traumatism have occurred, in which it is evident that the trauma merely made active a latent diabetes. This does not exclude the possibility that trauma alone may sometimes cause diabetes in man, any more than the absence of any observed association between diabetes and infection in dogs contradicts the demonstrated facts that infections aggravate human diabetes and that patients have been known to acquire diabetes with an infection and recover completely after the infection. The experiments prove that the ingestion of excessive carbohydrate or protein does not create diabetes but merely hastens its active onset. When the underlying tendency is slight enough, indulgence or avoidance

of dietary excess may be a deciding factor. These, in conjunction with former experiments, make it seem probable that luxus consumption of carbohydrate, nerve-strain, and other controllable influences may affect the incidence of diabetes by bringing out latent diabetic tendencies in a population.

The investigation of the role of fat in relation to glycosuria was undertaken along several lines. The proportion of pancreas which must be removed to induce diabetes in fat and thin[3] dogs cannot be shown to differ beyond the limits of experimental error and individual variation. The essential experiments consisted in depancreatizing dogs so that severe diabetes came on with or without overfeeding, and proving that the glycosuria could be stopped by fasting and kept absent on low diet at subnormal weight, while addition of fat to the diet brought on gain of weight and consequent glycosuria. These were the experiments upon which the undernutrition treatment was founded. The requirement was to make them conclusive. Accidental factors must be excluded, and it must be established whether the downward progress of such dogs is prevented or merely delayed. One possible method is to compare a sufficient series of undernourished dogs with the well-nourished dogs and learn which live longest and how the tolerance behaves. This was done, and in several undernourished animals a gratifying improvement of protein assimilation was observed in contrast to the downward tendency in the controls. But the undernourished animals fell victims to laboratory environment and the attempt had to be repeated. The longest duration was one year, with continued gain in tolerance and strength, which is not without importance. The undernourished state cannot be blamed for causes of death such as rabies, and badly undernourished street curs appear hardy. But in consequence of the accidents none of these experiments were long enough to found a fully decisive comparison. The ideal procedure would be to keep dogs sugar-free for a period on a given diet, then fatten the same dogs by adding only fat to the diet and show that glycosuria ensues, and then remove or diminish the fat and prove that glycosuria ceases and tolerance is raised. These experiments also were long, and were carried to the point where the obese dogs developed glycosuria. These were the first deaths in coma, which were important in opening up the study of acidosis, but highly inconvenient in the present connection through spoiling the chance of showing that the identical animals could be free from diabetes at reduced weight. On the whole the experiments along these lines were of a difficult and disappointing character, such as one would not wish to go through with again. Large pancreas remnants were requisite, in order that the dogs might retain appetite and digestion for fat. Animals must be chosen voracious enough to take hundreds of

[3] "Thin," in the ordinary sense, opposed to obese. Long fasting or extreme undernutrition makes a decided difference.

grams of sugar to break down their tolerance, and later to consume enough fat with restricted protein to become obese, as most dogs will not do. The preparatory period of sugar-freedom and fixing the tolerance was tedious, and after some months the dog might refuse to eat enough for fattening and have to be used for some other purpose. Few laboratories could be expected to repeat such experiments, and the outcome would still be subject to a personal factor. The results of briefer tests were in apparent contradiction to the longer experiments. Addition of fat to a diet causes a distinct depression of blood-sugar during digestion, confirming Jacobsen's findings in human patients. Dog 386 gives an example; Chart VIII shows how the blood-sugar was lower in every instance on protein plus fat than on the same quantity of protein alone. Intravenous glucose injections do not occasion higher glycosuria during alimentary lipemia than during fasting. The reports of Blum and Roubitschek that fat feeding increases adrenalin glycosuria could not be confirmed. The first part of the record of dog 356 (Table V) shows how feeding of only suet diminished the hyperglycemia in an animal with potentially severe diabetes. Even in the severest active diabetes the feeding of pure fat does not increase hyperglycemia or glycosuria. This statement is not altered by the experience that under some circumstances dogs with severe diabetes show a striking increase of blood-sugar after receiving fat; but though this increase may continue for several hours it may begin almost immediately, therefore is obviously not due to anything derived from the fat; and this view was confirmed by finding that an equal amount of kaolin or talcum powder has the same effect. It will be noticed that all the experiments of this order are inimical to the idea of sugar formation directly from fat. In the face of all the uncertainties and contradictions, there was a distinct belief that the long experiments pointed to fat feeding as a potent factor for producing diabetic glycosuria; but the question remained how to make this a positive conclusion instead of a personal impression.

Two changes were introduced. First, a slight increase in the staff permitted following the blood-sugar more satisfactorily. Second, independence of the dogs' caprice was gained by forcible feeding when necessary. The appetite of diabetic patients has never been the guide to their diet. Fat has been given to them disguised by all the arts of cookery, and in addition they have been ordered to drink olive oil and otherwise consume fat beyond their desire. It has not been found possible to fool the instincts and senses of dogs when they begin to revolt at fat, but it is feasible to stuff down a ration exceeding what most dogs will continue to eat voluntarily, and if properly planned it is well digested and absorbed. Since the highest fat gives the quickest results, the experiments are thus compressed into a few weeks or months and are convenient to repeat. The numerous controls show the absence of any similar results in dogs not subjected to the fatten-

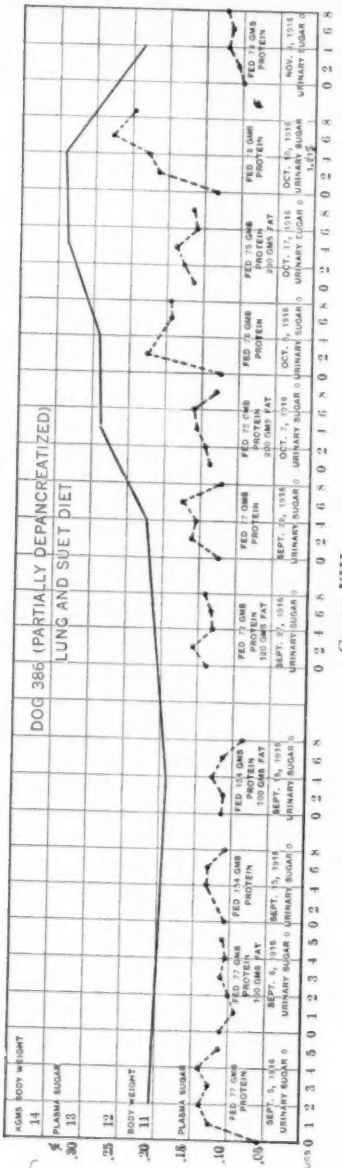
DOG 386 (PARTIALLY DEPANCREATIZED)
LUNG AND SUET DIET
KGMS BODY WEIGHT
PLASMA SUGAR
BODY WEIGHT
PLASMA SUGAR
HOURS
FED 77 GMS PROTEIN
SEPT. 6, 1916
URINARY SUGAR 0
FED 154 GMS PROTEIN
100 GMS FAT
SEPT. 15, 1916
FED 77 GMS PROTEIN
SEPT. 27, 1916
FED 75 GMS PROTEIN
200 GMS FAT
OCT. 7, 1916
FED 75 GMS PROTEIN
OCT. 15, 1916
FED 75 GMS PROTEIN
200 GMS FAT
OCT. 17, 1916
FED 75 GMS PROTEIN
NOV. 2, 1916
URINARY SUGAR 0

CHART VIII

ing process. At the same time successful experiments in which greedy dogs ate everything voluntarily show that the forcible feeding is responsible for no difference; and earlier experiences (above described) prove that the same thing happens when the ration is more moderate, only the time required is longer. Two examples of the recent type of experiments are here shown.

Dog 356 (Table V) underwent operation on July 13, which left a remnant of one-eighth to one-ninth of the pancreas. The tolerance was broken down by feeding, so that it was slightly below one kilogram of lung; that is, on feeding this quantity, glycosuria remained absent until the third day, then was 2.85 per cent. It was cleared up by two days of fasting; then on August 21 a diet lower in protein but higher in calories was given, namely, 400 grams lung and 200 grams suet. This dog had been in barely medium condition at her original weight of 15 kilos. The preparatory stage had reduced her to 11 kilos. The greatly undernourished dog ate all the suet eagerly, and tolerated this excessive ration without glycosuria, until on August 25 glycosuria of 2.6 grams appeared, with a fasting blood-sugar of 0.2 per cent. Here lung was omitted, and 400, then 300, then 200 grams of suet fed. Under this huge caloric intake, glycosuria ceased and the blood-sugar rapidly fell, giving no sign of sugar formation from fat. The protein was then cut far below the tolerance, and the fat diminished to what the dog could digest regularly. The normal plasma sugars from September 6 to 11 show that this diet of 150 grams lung and 200 grams suet was well within the tolerance at that time. Weight was steadily gained and the blood-sugar rose in parallel, while ketonuria and lipemia developed. The plasma sugar values on September 28 and 29 without glycosuria illustrate the renal impermeability under these conditions. On September 30 glycosuria developed. The diet at this time was changed to 200 grams lung, being approximately the former protein intake with omission of fat; and it was hoped that the course might thus be changed for the better. But the evil that fat does lives after it. A patient threatened with coma may not necessarily clear up if given a protein ration such as he subsequently may come to tolerate well after fasting; and when the injurious effect of fat has been pushed to this extreme point in diabetic dogs they are narrowly saved by using the same treatment as for human patients, although if the program had been changed earlier the simple omission of fat might suffice to reverse the progress. Accordingly, this dog was promptly fasted and there was prompt cessation of glycosuria and ketonuria. Low diet changed the condition so that the weight on November 3 was only 8.15 kilos, and 200 grams lung without fat caused no glycosuria, though the plasma sugar was 0.2 per cent., showing this ration to be still excessive. This is an example of treatment of severe diabetes by marked

undernutrition. When the dog was four kilos below medium weight the attempt to fatten her up to 3 kilos below the weight precipitated a dangerous diabetic outbreak, even though the gain was accomplished by addition of pure fat and there is no indication that sugar is formed from the fat. Not the kind of food given, but precisely the gain in weight above what the assimilative function is able to carry, is the cause of the breakdown in such dogs and in corresponding human patients. Life is saved by reducing the body mass to what the assimilative power is able to maintain, and if the sparing is adequate, more or less recovery of the function follows in all dogs and in the great majority of human patients. Such an undernourished state as required in this animal, though unpleasant in dog or man, affords the sole means available not only for averting impending death but also for opening the way to a better state. The diabetic has not the choice of a short and merry life versus a long and miserable one. By overtaxing his assimilation he brings on both shortness and misery of existence. These very thin dogs are stronger and happier than the fatter animals with glycosuria and acidosis; and the treatment of fasting and undernutrition for patients has brought not only improvement from the standpoint of laboratory analyses and expectation of life, but also comfort and usefulness and freedom from a multitude of complicating afflictions to a degree never before known.

In other animals as thin as this and with an equally low tolerance, in which the breakdown was produced by carbohydrate or protein, treatment by undernutrition has resulted in steady improvement, as manifested by ability to endure more food and more weight up to a necessary limit. Injury from fat is more lasting and dangerous, presumably because less obvious, so that the harmful process is at work unseen for a considerable time before treatment is applied. This dog 356 finally died in extreme emaciation after a course apparently representing spontaneous downward progress. It furnishes an exact parallel to the type of patients who finally die in spite of treatment, through failing to gain enough assimilative function to support life.

The graphic record of dog 386 (Chart VIII) gives a different example of the same principle. The dog came to the laboratory fat at a weight of 15 kilos, and the operation on April 28 left a remnant of only one-twelfth to one-thirteenth of the pancreas. Thus the tendency to diabetes was made more pronounced than in the preceding dog; but in consequence of more careful diet, for a longer period, the actual assimilation and condition were better. The tolerance was approximately 800 grams lung, which caused slight glycosuria on August 10, when the dog weighed 11.8 kilos, and no glycosuria on September 15, when the weight was about a kilo less. Meanwhile the regular diet was 400 grams lung, which was tolerated for a month without a trace of glycosuria. On September 18 the

diet was changed to 350 grams lung and 150 to 250 grams suet, which was continued except for a few test days for just a month. The animal behaved splendidly, enjoyed the diet throughout, and permitted a flawless experiment. The chart shows that at the outset the only indication of severe diabetes in a dog which seemed so beautifully healthy was the fact that protein feeding caused regularly a rise of blood-sugar like that produced by a large amount of carbohydrate normally. This is an interesting peculiarity of such animals. Not only the 400 grams of lung on September 5 and 6 was well borne, but also the 800 grams on September 15 and 16 caused no hyperglycemia greater than 0.13 per cent., thus proving the assimilation. Then the fat was added to the diet and the weight progressively rose. The chart shows how the fasting values for the plasma sugar were constantly within normal limits on the protein diet, also that where the plasma sugar was determined hourly or two-hourly after feeding the curve after protein plus fat was invariably lower than after the same quantity of protein alone. Nevertheless, as the weight rose the sugar curves also rose. On October 17 the regular protein-fat diet did not suffice for glycosuria, but on the next day the simple omission of the fat sent the plasma sugar so much higher that a glycosuria of 1.21 grams resulted. The attempt to carry this experiment through without fasting was unsuccessful, but on the usual treatment the glycosuria and the ketonuria also present promptly cleared up. On a low diet of protein the weight was brought down to 11.7 kilos, and a test on November 3 showed a fasting plasma-sugar of only 0.1 per cent. which rose only to 0.118 per cent. without glycosuria on the identical protein intake as before. As stated, the operatively produced tendency to diabetes is greater in this dog than in dog 356, but this one represents a case taken before it is so far advanced. This animal can be kept healthy and happy at as high a weight as necessary for either strength or symmetry. Obesity would bring on diabetes irrespective of the kind of food that produced the obesity.

In these and similar experiments one incidental observation is that the blood-sugar is not an infallible criterion for prognosis. It may be within normal limits both before and after meals on a diet which nevertheless is destined to make trouble later. Also, a very high level of blood-sugar may persist for a considerable time after wiser treatment has changed the direction of progress, so that hyperglycemia does not of itself demonstrate a breaking strain of assimilation or preclude improvement. A more broadly important lesson is that the age-long search of chemists for a magic food which diabetics shall assimilate perfectly is as vain as earlier quests of the holy grail or the fountain of youth or the philosopher's stone. What the diabetic organism is unable to assimilate without restriction is not any particular kind of food, but food as

such. From this standpoint all the attempts from the earliest ones with glycerin and lactic acid and levulose down to Rosenfeld's lactone and Grafe's caramel may be judged together and the true reason of their failure appreciated. It is not necessary to conclude that any component of fat is changed into sugar. Although Cremer and Lüthje proved the formation of sugar from glycerin, von Mering first and Lusk more exactly showed that fat feeding does not affect phloridzin glycosuria, and the latter found further that work, which increases fat catabolism, does not alter the D : N ratio, so there is entire lack of evidence that glycerin is split off from fat to form sugar. It may be significant that the experiments and theories of Embden, Neuberg, Dakin, Ringer and Woodyatt, however differing in details, stand in agreement regarding the conception of a merging and equilibrium of chemical products from different sources. It is known that certain substances participating in intermediary metabolism are chemically derivable from either protein, fat, or carbohydrate. Apart from the actual interconversion on a large scale possible between some of these substances, as amino-acids and sugar, it is conceivable that the mere glut of any products is a hindrance to either the anabolism or the katabolism of other products. In such embarrassment of the cells there are certain substances which most readily escape into the blood and urine; but it must not be concluded from this fact that the diabetic fault of assimilation is limited to sugar (as apparently in phloridzin poisoning) or that the intoxication of acidosis is merely due to the acetone bodies. Wells near the seashore rise and fall with the tide, not because any fresh water is derived from the ocean, but because the drainage of the underground streams is blocked in proportion as the tide is high. Such a comparison may explain the production of diabetic glycosuria by fat for those who do not believe in the derivation of sugar from fat. The primarily ketogenetic and secondarily glycosuric action of fat and the primarily glycosuric and secondarily ketogenetic action of carbohydrate are in accord with this speculation. Janney's investigations of proteins cannot show that any amino-acids are harmless, but may indicate which of them are preferable in cases in which the principal immediate tendency is to glycosuria and in others in which the existing tendency is to acidosis.

The most important fact shown by this series of experiments is that the appearance of spontaneous downward progress observed in human patients can be exactly imitated in dogs. It is possible that further factors, notably occasional infections, may be operative in at least some human cases. It is not positive that the undernourished dogs will be able to live indefinitely. But it is conclusively demonstrated that the attempt at high nutrition, even with fat, produces in these dogs an appearance of spontaneous aggravation of condition as striking as anything witnessed in

human patients, and that this result can be prevented at least for periods of years by limiting the total caloric intake and the body mass to correspond to the assimilative function. The experience with diabetic dogs warns unmistakably against efforts to maintain patients on a luxus level of diet or weight. The standard should approach that of Chittenden rather than that of Voit. Restriction of single foods, as carbohydrate or protein, suppresses symptoms temporarily, but lightening the total load upon the weakened assimilative function is the only present means by which it may be hoped actually to halt the diabetic process.

The animal experiments have placed the successful therapeutic results on something more substantial than an empiric basis, independent of opinions or impressions, and no clinical mishaps, whether due to faulty application of the method or to failure of a defective function to recover by rest, can now shake the principles on which this treatment is founded or justify a return to overfeeding with fat and other mistakes of the past.

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ENDOTHELIOMA OF THE RIGHT BRONCHUS REMOVED BY PERORAL BRONCHOSCOPY.[1]

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The patient was referred to the author by Dr. J. P. Harley, of Williamsport, Pa., who stated that there were signs of a localized

[1] Read at the Meeting of the American Laryngological Association, May 10, 1916.

pathology in the right bronchus and right lower lobe which, in his opinion, was not tuberculous and was otherwise so unusual as to demand a diagnostic bronchoscopy. The patient's statement (to Dr. Harley) that he had "a sensation as of a 'ball valve' in the right bronchus shutting off his breath, at times when breathing in, at other times when breathing out, impressed the author with the idea that the patient was a neurasthenic, in view of which a diagnostic bronchoscopy did not seem justifiable. The outcome showed this opinion erroneous. The following is the history:

CASE HISTORY.—Mr. F., aged thirty-five years, occupied as a clerk at a desk and around a factory, had had good health until five years ago. Ill health started with a "heavy cold" lasting one year; then he spat blood. Symptoms were less during summer. Every winter's end and spring, symptoms were worse, starting as "heavy cold" and ending in ill health. Patient refers sensations ("restriction, swelling, compression, wheezing") to his right side. Wheezing audible with mouth open, worse after expectoration. Breathing never seems normal. Has sensation of secretion in bronchi, also sensation of "flapping" at times. Also a sensation as of a ball valve suddenly shutting off sometimes inspiration, at other times expiration. Twice yearly has cycle of the following symptoms in the order given: (1) Cold in head. (2) Tightness in chest. (3) Cough. (4) Slight expectoration. (5) Free expectoration. (6) Bleeding, which formerly amounted to about a fourth of a cupful, and was followed in a few days by expectoration of blood clots. Recently only blood streaks were noticed in expectoration.

He spent two years in a sanatarium for the tuberculous. Discharged because no bacilli could be found in sputum, but cough and wheezing persisted. Roentgen-ray examination and sputum examinations, guinea-pig inoculation, Wassermann and therapeutic luetic tests at a large eastern hospital, were all negative. Diagnosis then made: enlarged bronchial gland. No treatment was beneficial. No sputum test had been made during the last twelve months. Bronchoscopy by someone was negative. Septum deflected by "foul tip" at basball some years previously. Septal operation by Dr. Ritter cured persistent headaches.

Diagnoses of various clinicians prior to coming under observation of Dr. Harley were: tuberculosis, chronic right-sided bronchitis; monolateral (right) asthma; compression stenosis of right bronchus, probably caused by adenopathy. Dr. J. Chalmers Da Costa had made what ultimately proved to be a correct diagnosis of obstruction of the right bronchus.

Report of Sputum Examination by Dr. Ernest W. Willetts. "Very careful repeated examinations for tubercle bacilli both by direct smears and also by antiformin method failed to show them. The sputum contains some small whitish masses of solid matter, which, on examination, showed many large cells of varying shapes. Some

oval, some spindle-form and others polygonal. They are unlike any of the cells ordinarily seen in sputum and are so like cells from a new growth that a diagnosis of tumor is, I believe, justifiable."

Report of Dr. George C. Johnston. First Fluoroscopy. Fibrosis of right lower lobe bronchus. Patient presented symptoms of unilateral asthma on fluoroscopic examination. Left lung and diaphragm normal; parts were normal in size, shape, and position. Right upper lobe normal, but beginning about one inch below bifurcation a trefoil-shaped shadow extending downward was seen. The diaphragm on the right side could not be distinguished. The lower lobe of the lung was replaced by a shadow having exactly the opacity of the liver. It was impossible to state where the liver ended and the lung began. The appearance was that of an unresolved pneumonia. This portion of the lung could not be made to light up on deep respiration or coughing. No motion of the right portion of the diaphragm could be seen nor could its position be located.

Second Fluoroscopy. At a second examination two days later a considerable change had occurred. Some portions of the dense shadow were clear, showing that the lower lobe was occasionally receiving small quantities of air. The diagnosis of atelectasis due to right bronchial obstruction was made, and diagnostic bronchoscopy was strongly urged.

Roentgenographic examination (Fig. 1) showed an opacity of the lower lobe continuous with the hepatic opacity, the dome of the diaphragm on the right side being indistinguishable.

Physical Examination by Dr. John W. Boyce. At the date of the first examination there was some contraction of the right side and a slight impairment of percussion note, both of them corresponding to extreme expiration as though the air could not get in. Vesicular sound was suppressed and replaced by large wheezing rales. There was evidently obstruction in the right main bronchus, affecting inspiration more than expiration at this particular time. There was some impairment of supracardiac resonance and also an increased area of conduction of whispered voice at the back; but both of these signs (suggestive of bronchial adenopathy) extended rather to the left than to the right.

Aneurysm or other mediastinal tumor having been excluded, we have to consider the possibility of a single lymphatic gland making pressure on the bronchus. This diagnosis has been suggested by an expert clinician. Against it is the fact that there is no evidence of bronchial adenopathy. Nor can we conceive how pressure from without could exert a valvular effect, occasionally reversing the direction of the valvular action. The same considerations apply to organic stricture almost hermetically tight, large caliber strictures being latent as regards dyspnea. The long duration of attacks seemed to exclude spasmodic stricture.

It remained then for us to consider transparent foreign body and pedunculated intrabronchial growth. Dr. Jackson theoretically excluded the former on the ground that a movable foreign body in the open bronchus would certainly produce purulent sputum and foul breath in less than five years' time. This narrowed down the diagnosis to a movable intrabronchial tumor. The only objection to this diagnosis is, as Dr. George C. Johnston expressed it, that it "explained every item of the history and physical examination too nicely." Clinical diagnoses and pathological conditions rarely fit so precisely.

Bronchoscopy. Under local anesthesia I passed a 9 mm. bronchoscope. A moderate amount of secretion was encountered coming upward from the right bronchus. When this was cleared away and the bronchoscope was inserted into the right bronchus to the point where the image shown at B, in Fig. 2, should normally appear the tumor (A) came into view. The tumor filled a dilatation of the right stem bronchus and sprang from the right bronchial wall, just above the orifice of the middle-lobe bronchus.

The history of five years' duration, the smooth shining surface, slightly nodular shape, and the fact of the tumor having made for itself a dilatation of the bronchus, lead the author, in consultation with Dr. Ellen J. Patterson, to conclude that the growth was benign, probably fibromatous, and to advise immediate removal without withdrawal of the bronchoscope. The patient gave his consent by a slight nod, and the growth was extirpated in a few minutes by successive nips of the bronchoscopic tissue forceps. The bleeding was not severe; possibly as much as two ounces of blood were expectorated. The temperature rose to 102.2° F., the pulse to 98, the respirations to 30. All came to normal in about one week. Expectoration of blood-stained pus gradually diminished until it disappeared at the end of about four weeks. The patient has had uninterrupted good health until the present time—nine months. The present condition of the patient is thus reported by Dr. Harley:

"In replying to you regarding Mr. F's. condition, I wish to say the word "fine" does not half express his good condition. He has gained twenty-six pounds in weight; has enjoyed the best health this winter for six years, not having the slightest bronchial affection all winter; just feeling at the "top of the heap" ever since his operation. I feel sure he is grateful to you every day of his life for this most remarkable cure."

Report of Histological Examination of Tumor by Dr. Ernest W. Willetts:

"Frozen sections show a very cellular structure which presents the general appearances of an endothelial growth, although in some areas there are appearances that indicate epithelial origin. Nuclear changes are not marked, but the growth is so cellular and infiltrates

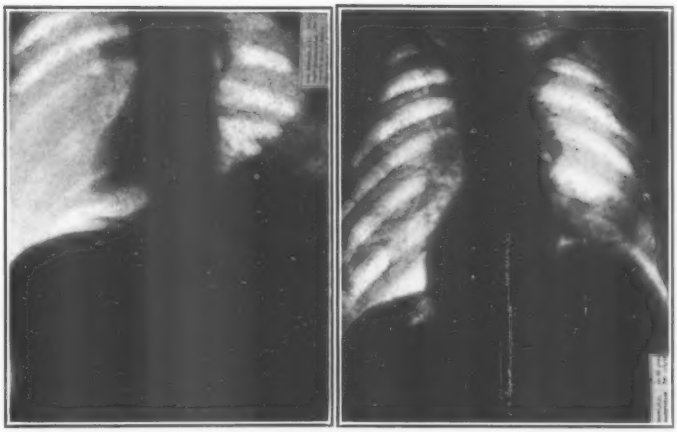

FIG. 1.—Roentgenogram showing (on left) opacity of lower lobe of right lung, due to obstruction of right bronchus by tumor shown in Fig. 2. The right-hand side of illustration shows roentgenogram taken after peroral bronchoscopic removal of tumor.

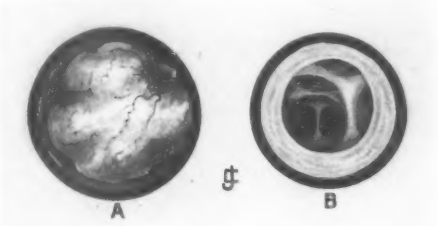

FIG. 2.—Endobronchial obstructing endothelial tumor in a man, aged thirty-five years, who complained of coughing, wheezing, and "a sensation as of a ball valve shutting off his breath, sometimes on inspiration and at other times on expiration. *B*, bronchoscopic view down right main bronchus. *A*, tumor presenting itself in its self-made bronchial enlargement, when the bronchoscopic tube-mouth reached the location at which the view *B*, should appear. Tumor removed with forceps through a bronchoscope passed through the mouth. Patient free from symptoms at end of three weeks and remained perfectly well a year and a half later.

the supporting tissues in such a way as to suggest malignancy. Later examination of paraffin sections only confirms original opinion."

REMARKS. In discussing the paper of Dr. J. M. Ingersol at the meeting of the American Laryngological Association in 1914, I spoke against the attempt at bronchoscopic removal of endotracheal malignancy; and such being my conviction, I would not have removed the endobronchial growth in the present case had I not felt at the time that it was benign. The present condition of the patient, however, indicates that Dr. Ingersol's position as to the possibilities of bronchoscopic removal may be nearer right than my own, though he referred only to tracheal growths, while my case was bronchial. It would not be right, however, on the basis of this unique case, to sanction the indiscriminate bronchoscopic attack of pulmonary malignancy. It seems scarcely possible, bronchoscopically, to remove malignancy completely in many instances; and we all know only too well the results of partial removal elsewhere. So far as the present case is to be taken for guidance, it can apply only to a sharply circumscribed non-ulcerated tumor of very slow growth. Moreover, it may be that the tumor was one of those that is histologically malignant and clinically benign. Or, it may be that it was of a very low degree of malignancy, for we know that there are degrees of malignancy or of individual vulnerability; and, as stated by Wright, it is not possible to make a prognosis from the histological examination of a growth. Finally, we know that recurrence is yet possible. In view, however, of the very great rarity of the case and the necessity for us all to be alert to the possibilities of diagnostic bronchoscopy, longer delay in making this report seemed inadvisable, especially in view of the fact that the present condition of the patient and his months of perfect health fully justified the relatively minor operation under local anesthesia, even if the growth ultimately recurs.[2]

CONCLUSIONS. 1. Diagnostic bronchoscopy is indicated in cases of monolateral "asthma," bronchitis, bronchial obstruction, and in cases of tuberculosis where persistent search fails to show tubercle bacilli.

2. Peroral bronchoscopic removal of an endobronchial tumor is feasible under local anesthesia.

3. General anesthesia might have permitted clotting of blood in the lower bronchi before bechic expulsion, involving septic risk.

4. Peroral bronchoscopic removal may be justifiable in a malignant endobronchial growth if small, circumscribed, and not ulcerated.

5. As this is the only recorded case of apparent cure of an endothelial endobronchial tumor by peroral bronchoscopy, and only the second endoscopic removal of any form of malignant growth from a bronchus, it would be unwise to make too many or too sweeping deductions.

[2] One and one-half years have now elapsed and the patient is in perfect health, without expectoration or any other symptom.

"SPELTER CHILLS."[1]

By David Riesman, M.D.,
AND
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(From the Medical Division of the Philadelphia General Hospital.)

In recent years the results obtained from the study of occupational diseases has been most gratifying. Such a study not only often aids in arriving at an otherwise difficult diagnosis, but as a part of industrial hygiene it has become of great importance in the prevention of those ills that are the result of occupation.

With this in mind a systematic study of occupational diseases is being made in the medical division of the Philadelphia General Hospital, and the affection about to be described is one of a number of interesting conditions revealed by this study.

"Spelter chills" is the name given to a condition heretofore but briefly described under such varying terms as brass-founders' ague, brass chills, zinc chills, smelter shakes, das Giesfieber or Staubfieber, and fièvre des fondeurs. We believe the condition results from the inhalation and ingestion of the fumes and flakes of zinc oxide arising from the melting and volatilizing of spelter, which is the commercial name for zinc in its impure state. Spelter chills we found to be the name popularly employed among the local workmen.

The chills occur in brass foundries, in zinc smelters, and in places where zinc is poured. The majority of instances are found in places where yellow brass is manufactured, a process in which a large percentage of zinc is used. The chills do not occur in those engaged in processes in which the zinc is not volatilized. Lehman produced it artificially in a workman by burning zinc. Some investigators have suspected copper as the cause of the chills. This seems unlikely in view of the fact that in the manufacture of red brass, which contains a large percentage of copper and a small percentage of zinc, the chills occur less frequently than in the manufacture of yellow brass, which contains a greater percentage of zinc than of copper. In brass workers employed in finishing or polishing of brass, though they inhale quantities of copper-laden dust, as is shown by the excretion of copper in the perspiration imparting a greenish tinge to the skin, hair, and underclothes, the chills never occur. Lead as a contributory cause may be considered a negligible factor.

A brief description of the process which exposes the workers to

[1] Read before the Section on General Medicine of the College of Physicians of Philadelphia, March 27, 1916.

this ailment may be of interest: Zinc is obtained from its ores, zinc sulphide or zinc blende and zinc carbonate or calamine. Brass is ordinarily of two varieties, red and yellow. The red brass, the better quality, is made up of from two to four parts copper and one part zinc. The yellow brass is made up, roughly, of three parts copper and two parts zinc. The relative proportions of zinc and copper thus determine the quality of the brass.

Brass is manufactured by either the direct or the indirect process, the latter being the safer, though the former is probably in more common use. In the direct process the metals are all fused together at the same time. In the indirect they are fused one after another, the order depending upon the relative fusibility and volatility. The metals are melted in a large crucible, which is first heated to avoid breaking. Into the crucibe is put, first, a mixture of scrap brass or grain copper; rarely are the pure copper and zinc directly mixed in their definite proportions. After the material is melted down the proper amount of copper or zinc is added to secure the desired composition. It requires 2000° F. to melt copper and 770° F. to melt zinc. Hence the necessity of adding the zinc last. Zinc is readily volatile above 770° F., and for this reason must be well submerged beneath the surface of the melted copper. The mixture is then poured into molds. Though the process up to this point exposes the workmen in some degree to the metallic fumes the pouring is probably the source of greatest danger. As the metal is being poured the atmosphere becomes laden with intensely irritating whitish fumes and fine flaky deposits of zinc oxide or "zinc snow," as it is called. Sir Thomas Oliver gives the following analysis of this "zinc snow":

Moisture	9.64
Organic matter	39.42
Silicious residue	9.14
Oxide of zinc	28.82
Oxide of iron	2.78
Copper	1.71
Other matter	8.49
	100.00

Another analysis gives 44.9 per cent. zinc.

It is this volatilized zinc or "spelter" impregnating the atmosphere breathed by the workmen that we think is the cause of the "spelter chills." As to their ultimate cause we are not prepared to speak. Lehman believes the symptoms are due to an auto-intoxication from absorption of dead epithelial cells lining the respiratory tract, the cells being destroyed by the inhalation of zinc oxide fumes. Rambouse says that neither pure copper nor pure zinc gives rise to poisoning, yet the pouring of brass, an alloy of zinc and copper, sets up a peculiar train of symptoms. The question of infection seems doubtful. It is probably an acute intoxication.

Thackrah in England, in 1830, recognized a definite train of symptoms arising from the inhalation of volatilized zinc, but makes no reference to the chills. Greenhow in England, in 1845, described a condition "similar to an intermittent fever of an irregular type." Blaudet and Greenhow were also aware of a form of poisoning observed in brass pourers. The chills themselves seem to have been first observed by Schwitzer, in Germany, in 1862. The observations of Siegel made in Wurttemberg in 1905 are, however, the most valuable on the subject. Rarely has the condition claimed the attention of American writers, a few reports of individual cases only having been made in Chicago, in 1904, by Drs. Ungre and Savin and by Dr. S. R. Pietrowiecz. Dr. Kober comments on it in his report to the House Commission. Dr. Hayhurst in his "Report on the Investigation of the Brass Manufacturing Industry in Chicago" contributes the most elaborate American report.

Conditions Predisposing to Chills.—Respiratory and circulatory disturbances favor a more sudden and severe onset of the chills. Minors and women and those unaccustomed to the work are more susceptible than others. Alcoholism, anemia, malnutrition, and impaired renal function likewise constitute predisposing causes.

Characteristic of the chills is their tendency to attack the workmen every Monday. This may perhaps be due to the free indulgence in alcohol over the week end. The chills occur most frequently in winter, this undoubtedly being due to the greater accumulation of the fumes in the workshop owing to the windows not being open. Their frequency is further increased on damp, cloudy days on accountof the heavy atmospheric conditions and consequent difficulty in clearing the room of the fumes.

Description of the Attack.—The chill may begin while the man is at his work in the latter part of the afternoon and after the second pouring, but more often it begins soon after leaving the shop or in the early evening. (This we think is due to a diminished activity of the sweat glands after leaving the overheated shop.) Free perspiration, by favoring an excretion of zinc, not only aids in aborting the chill but noticeably diminishes the intensity and duration of an attack. For this reason the men resort to hot drinks, the most efficacious, one of our patients told us, being hot milk with red pepper. For the same reason the men wrap themselves in blankets.

The first thing complained of is a creepy, chilly sensation up and down the spine which gradually extends throughout the entire body. It may continue as a mere chilliness, but more often develops into a genuine rigor which lasts for from one-half hour to an hour or even from two to three hours. At its height, cramps and pains in the limbs are apt to occur; abdominal pain is infrequent, except as it may follow the ingestion of cold drinks. The pulse is increased in frequency and there is a slight elevation of temperature. Preceding the chill there is a dry, scratchy sensation in the throat, a sticking, pricking feeling

in the tongue, oppression in the chest, and an irritating cough, usually unproductive. Actual dyspnea is rare. There is a feeling of prostration and of nausea which frequently eventuates in severe vomiting. Diarrhea is common; indeed, the men at all times have a tendency to diarrhea, constipation being rare among brass molders. As the attack subsides the patient, quite exhausted, breaks out into copious perspiration and soon falls into a deep sleep. A temporary loathing for food and an unpleasant metallic taste in the mouth are present on awakening and last a little while.

One of us exposed himself for two afternoons to the fumes and flakes of zinc oxide during the melting and pouring process. In a few minutes the above-mentioned irritative condition in the throat and chest, with coughing, was experienced. Headache also developed, and later a slight diarrhea. No chilliness, however, was felt.

The attacks do not often incapacitate the workers. For this reason, and also because the men accept the "chills" as a matter of course and of no moment, the physician rarely has the opportunity of witnessing an attack. Great numbers of these workmen, it is reported, visit the out-patient department of the Birmingham Hospitals, but always for respiratory and digestive disturbances.

It is doubtful if single attacks of this affection are of any importance, but repeated again and again, as they usually are, sometimes for many years, they undoubtedly produce far-reaching effects in the human economy.

Among the chronic manifestations of the intoxication, those pertaining to the pulmonary system are the most serious. Brass-founders are especially subject to bronchitis and phthisis, and frequently succumb to pneumonia. A very high death-rate from lung diseases is recorded among the Berlin founders.

A tendency to arthritic attacks with acute and chronic joint manifestations we feel has been somewhat overlooked. One of our patients at present is convalescing from a severe attack of acute inflammatory arthritis complicated with an acute endocarditis and pneumonia. Another suffers with chronic arthritis deformans, and still others have repeatedly complained of mild though definite joint symptoms. Gastro-intestinal disturbances are common; among the more ordinary are attacks of anorexia, headache, apathy, epigastric distress after eating, nausea, and diarrhea. Jaundice sometimes occurs. We have knowledge of an especially interesting case of jaundice which we feel was directly due to zinc intoxication. Unfortunately, we were not able to study it. Among his coworkers the man was known as "yellow-brass Rudy." He was especially subject to the chills, and became markedly jaundiced within a few hours after pouring yellow brass. He could pour red brass without much disturbance, but would not accept, if he could help it, a position where he had to handle yellow brass.

Among the other ill-effects of this vocation we noted a state of malnutrition, a pasty, sallow complexion, and a slight secondary anemia. (The blood cells showed no "stippling.") A well-developed pyorrhea alveolaris was present in all the cases. We detected no changes in the central nervous system, though tabetic symptoms are said to occur. Chronic renal disease should be looked for. Kober found that zinc workers may excrete zinc for months in the urine, though often without signs of poisoning, and Weyl mentions a case showing albumin and a trace of zinc in the urine after a chill. No albumin could be demonstrated during the time the patient was free of the chills. Siegel found a trace of zinc, but makes no mention of albumin in the urine after a chill. Goodman demonstrated the presence of copper, but not of zinc, in the urine and sweat of a brass-worker. The man was probably a finisher and not a molder. As mentioned before, brass-finishers and polishers frequently show visible evidence of copper excretion in the sweat (*i. e.*, greenish tint to skin and hair, staining of underwear, and aggravated itching of the skin). These symptoms are all due in a large measure to uncleanliness, and frequent bathing and the free use of talcum powder tend to prevent their occurrence. The men are not particularly unhealthy.

As the result of examinations kindly made for us by Drs. John Marshall and Wertheim, we are able to report that analyses of the urine from a number of cases revealed no zinc or copper.

It seems that no great tolerance for zinc is ever acquired. Men who have been in the trade for twenty-five years and more frequently suffer from the chills. Certain individuals are more susceptible than others, developing a well-marked chill almost every night and a particularly severe one on Monday nights. None of the subjects experienced the chills when not engaged in their work. About 75 per cent. of the men exposed develop the chills. The general mortality rate among these workers is higher than that among other workmen. One authority says it is two and a half times that of farmers. Sir Thomas Oliver notes that "only ten brass-workers were found living out of 1200 casters in Birmingham who were past sixty years of age, and that a superanuation insurance for brass-founders to begin at fifty-five years of age had only three applicants in a period of some ten years." Hayhurst noted that from among 1761 foundry men the oldest at the trade was seventy-three years of age, that only 17 were past fifty, that 60 were past forty-five, and 180 past forty years of age.

General Conclusions.—Spelter chills lie in the field of preventive medicine. To eliminate them the following precautions should be observed on the part of the employer:

Guard against inhalation and ingestion of metallic vapors by providing the working rooms with an efficient system of ventilation practical for all seasons of the year.

Keep the furnace room apart from the others and provide proper ventilation about the furnaces.

Employ an improved technic for pouring when such is at fault—perhaps some automatic device.

Provide for the removal of all metallic dust and deposits about the foundry by a systematic and thorough cleansing, at regular intervals, of the floor, walls, ceiling, rafters, etc.

Employ strong, healthy men to do the work demanded in brass foundries, zinc smelters, and in any allied trades in which zinc is poured.

Do not employ minors or women.

Do not demand of the workmen an amount of labor that is fatiguing.

Provide proper washing and toilet facilities, and advise the men as to the necessity of their proper use.

Allow the men reasonable time for washing before their eating period and a suitable place for eating.

Caution them to change their clothes before leaving the shop. Advise them not to wear mustaches and to employ respirators when necessary. Caution them against sudden changes in temperature.

A study of industrial diseases is of great importance and should form part of the curriculum of medical schools. With the help of the State, which is now assured in Pennsylvania and in several other commonwealths, it will be possible to inaugurate methods of prevention that will greatly lessen disease and increase the efficiency of the workers.

UNILATERAL RENAL HYPOPLASIA AND DYSPLASIA DUE TO DEFECTIVE ARTERIOGENESIS; RELATION TO SO-CALLED HYPOGENETIC NEPHRITIS.[1]

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The facts embraced in this communication are presented in support of a contention that there is a type of renal anomaly of developmental origin which predisposes to or renders inevitable some form of nephritis, and that this congenital abnormality is probably primarily a defective arteriogenesis necessarily early in the evolution of the organ; furthermore, it is thought that some evidence, based on morphology, is here presented for the first time. The material upon which the report is based represents an accumulation of four years. In order to establish the thesis enunciated it is

[1] Read at the meeting of the Association of American Physicians, May, 1916.

necessary to prove (1) that abnormal kidneys reasonably assignable to such a group occur; (2) that they result from defective arteriogenesis; (3) that they are accompanied by, or lead to, cardiorenal phenomena in at least some degree reasonably attributable to the kidney condition.

Kidneys of the type considered have long been known and variously named, and the congenital origin of many fully accepted. Chopart[2] knew that one kidney might be large, the other small. The earlier observers did not differentiate congenital or primary hypoplasia from sclerotic, inflammatory and other forms of secondary contraction, or atrophy. Indeed the term atrophy, frequently used, is not acceptable; it implies wasting. Some of these kidneys have at no time been larger than when found; such are not wasted organs. As applied to these organs the terms rudimentary, fetal and infantile are also of uncertain interpretation. Teyssèdre[3] used the term renal agenesis; hypogenesis is better. Agenesis should mean absence of the organ, often, however, it is used synonymously with hypogenesis.

LePlay and Fayor[4] call the condition renal disparity and observe that it is an arrest and not an atrophy. Evidently Gastaldi[5] has the same thought and terms it inequality of renal volume, and congenital unilateral atrophy; he restricts these names to kidneys in which both vessels and ureters are present. Braasch[6] evidently recognized this type of lesion, which he included under unilateral atrophic kidney and thought it might be congenital or acquired. Cadore[7] and Gerard[8] include relative atrophy obviously meaning abnormal smallness of one kidney and apply the term absolute atrophy to a more marked lesion. Polack[9] describes the condition of agenesis. Many so-called discoid kidneys[10] belong with this group. Some infantile kidneys of the type described by Geraghty and Plaggemeyer[11] should also be included. The organs and clinical phenomena to which Babes[12] applied the term hypogenetic nephritis and the forms studied by Mironescu[13] and by Jianu and Meller[14] have to do with this type of lesion. The condition is recognized by most authors of text-books; kidneys like those constituting the basis of this article are known to, and adequately described by

[2] Maladies des Voies Urinaries, Paris, 1830; cited by Gastaldi.
[3] Thèse de Paris, 1892.
[4] Bull. et Mém. de la Soc. Anat. de Paris, 1909, T. 84, 339.
[5] Thèse de Paris, 1910.
[6] Ann. Surg., 1912, lvi, 726.
[7] Thèse de Lille, 1903.
[8] Jour. de l'Anat. et de la Physiol., 1903, 39th year, 176.
[9] Thèse de Bordeaux, 1908.
[10] Fèrè, Bull. de la Soc. Anat. de Paris, 1881, 417; Legueu, Bull. de la Soc. Anat. de Paris, 1892, 19.
[11] Jour. Am. Med. Assn., 1913, lxi, 2224.
[12] La Sem. Med., February 8, 1905; cited by Jianu and Meller.
[13] Beit. zum Studium der Histologie der hypogenetischen Nephritis (rumanisch) Bukarest, 1908; cited by Jianu and Meller.
[14] Centralbl. f. allg. Path. u. path. Anat., September 15, 1912, 774.

practically all systematic writers; the basis of defective angiogenesis, however, is not presented as the essential factor in their evolution.

These kidneys are hypoplastic or defectively developed organs; often they are more, the internal arrangement of cortex and medulla is quite anomalous (see Figs. 1, 2, 3, 5, 7), a sort of dysplasia or cacoplasia.

Morbid Anatomy. Although both organs may be involved, hypoplasia is rarely, if ever, bilateral and even where both kidneys are implicated is never truly symmetric; commonly it is restricted to one kidney, the other showing compensatory hypertrophy. Usually the affected organ weighs one-fourth or less, to one-half as much as the other. In five instances I have the weights of both kidneys; the average for the smaller organ is 75.8 gm., and for the larger 140.4; if two cases in which both kidneys are obviously affected be excluded the average weight of the larger kidney becomes 161.3 gms.; the average for the smaller is but little influenced, being 75.4 gms. The most marked difference in weight is 110 gms., the larger weighing in this case 210 gms., the smaller 100 gms. In four cases the smaller kidney weighed 20, 35, 50 and 60 gms. respectively. Teyssèdre[15] observed an instance in which the involved organ weighed 0.85 gm. Gastaldi[16] from computations based on original observation and collated data gives for a man a normal of 152 gms., for left kidney, and 141 gms. for the right.

It is, therefore, obvious that the affected kidney may weigh less than 1 gm. and anything between that and the normal. The whole kidney need not be involved (several kidneys show this, notably the upper in Fig. 5); one pole may be practically normal or at most but little affected. Anomalies of the genitalia[17] usually unilateral and on the side of the hypoplastic kidney, frequently accompany renal anomalies of this type; in case recorded by Lombroso[18] the renal defect was on one side and the genital abnormality on the other. Renal dystopia and misplacements of ovaries or testes have also been noted.

The accompanying reproductions (Figs. 1 to 6 inclusive), from photographs, are, in each instance, one-half normal size and adequately illustrate the gross morbid anatomy. An epitome of known data is included in each legend. I have photographs of all specimens studied; this publication includes a few typical specimens only. With the exception of one pair all the organs are in the Museum of the Jefferson Medical College. As much histologic description as may be necessary to present the vascular changes and their results will be given when discussing defective arteriogenesis.

Of Gastaldi's 66 cases, 10 were females, 32 males and in 18 the sex was not stated. In my series 5 were males, 4 females. Including

[15] Loc. cit. [16] Loc. cit.

[17] Secher, Berl. klin. Wchnschr., 1915, 52d year, 487; Jainu and Meller, Centralbl. f. allg. Path. u. path. Anat., September 15, 1912, 774; Besançon, Thèse de Paris, 1889.

[18] Cited by Winter, Arch. f. klin. Chir., 1903, Bd. lxix, 6111.

the 9 cases on which this report is based, 60 cases have been identified in which the kidney involved is known: 32 right, 28 left. Of 9 patients here reported 3 were negroes.

FIG. 1.—Incised surface of kidneys, neither normal; upper organ of infantile type. One-half natural size. M. J.; female; white; aged seventy-three years. Patient and husband insane. Arteriosclerosis; tuberculosis; tuberculous peritonitis. Cardiorenal symptoms (dropsy, stupor, uremia); death. Urine pale: specific gravity, 1010: albumin and casts. Postmortem: Arteriosclerosis. Heart 510 gms. Right kidney (upper) 20 gms. Left kidney (lower) 120 gms. Duplicated renal vessels on both sides. Right kidney of infantile type; vessels nearly obliterated. Distinctions between cortex and medulla imperfect and arrangement abnormal in both organs. Open aorta with abnormal orifices of renal arteries above and to left. See also photograph of other aspect shown in Fig. 2. (Museum No. 1637.)

Concerning the second proposition, namely, that the abnormal kidneys result from defective arteriogenesis, the evidence must be more carefully weighed. The time is past when doubt as to the vascular origin of certain forms of nephritis can be entertained; arteriosclerotic kidney is universally accepted. When, in this condition, one kidney is much more changed than the other, or one

renal artery more sclerotic than its mate, or, as is not unknown, when a branch of one renal artery, distributed to one pole of one kidney, is more sclerotic than other branches to other parts of the same kidney, is it not reasonable to assume that some congenital or essential developmental peculiarity has determined the asymmetric

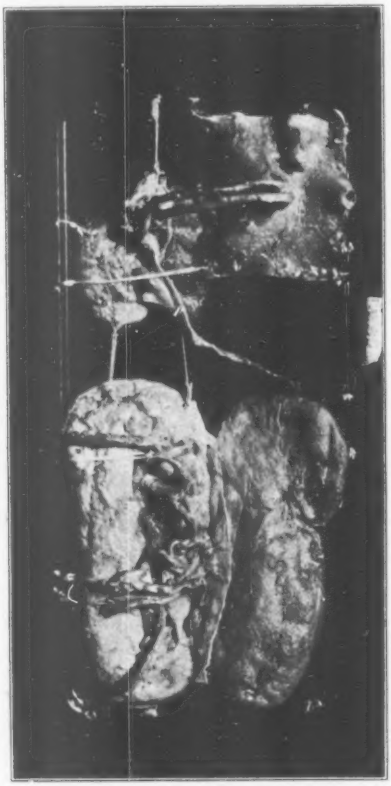

FIG. 2.—One-half natural size. External aspect of opened kidneys shown in Fig. 1. Above and to right external aspect of opened aorta. Smaller kidney supplied by two renal arteries both small and cord-like. Artery to larger kidney came off from aorta as a single trunk dividing at once into two branches both of which are shown on left half of lower organ. Trunks and branches show notable sclerosis superimposed on a congenital anomaly. Clinical data are given in text and in legend to Fig. 1. (Museum No. 1637.)

distribution of the lesion? The pressure in both arteries must be balanced, the toxicity of the blood, the irritant, destructive or other noxious agents in that fluid must be proffered alike to both arteries and to all branches of the same artery, so that if differences are found the reasonable assumption is that they resulted from peculiarities of the affected vessel. Resting on known facts deduction necessarily

leads to the conclusion that developmental peculiarity must be a determining factor.

For about a quarter of a century through succeeding editions, Osler[19] has maintained that some patients have better vessels than others; it is reasonable to believe that in the same patient some

FIG. 3.—Both organs hypoplastic and dysplastic; superimposed alterations of secondarily contracted (arteriosclerotic) kidneys. One-half natural size. Female; colored; aged thirty years. Brought to Hospital in convulsions; unconscious; unequal pupils; urine contained albumin. Coroner's case. Death attributed to septic embolism from infected finger. Postmortem: Pneumonia; pleurisy. Heart weighed 350 gms. No evidence of embolism and no thrombosis found. Moderate arteriosclerosis. Right kidney (upper) 50 gms. Left kidney (lower) 130 gms. Distinction between cortex and medulla possible at points only. (Museum No. 615.)

arteries may be better than others. Lancereaux[20] clearly recognized a relation between congenital narrowing of the vascular tree

[19] Principles and Practice of Medicine, 1892, 664; Osler and McCrae, Principles and Practice of Medicine, 1916, 8th ed., 842.

[20] Art. Rein. du Dict. Encyclop. des Sci. Med., 1876, 3me Serie, T. 3, 216.

and nephritis, observing that in some patients the former is at first accompanied by chlorosis, and later by albuminuria with atrophic sclerous nephritis. Gaucher,[21] Rayer[22] and Besançon,[23] contended

FIG. 4.—Presented through courtesy of Prof. Stengel, Prof. A. J. Smith and Dr. Weidman. One-half natural size. E. H.; female; white; aged twenty-one years. "Always had kidney trouble." In 1912 when six months pregnant, toxemia, albuminuria, miscarriage. January, 1914, therapeutic abortion for toxemia, albuminuria, etc. Blood-pressure known at that time to exceed 212. Recovery with high blood-pressure. Readmitted in August and again in December, 1914. Quantity of urine varied from 750 c.c. to 2825 c.c. Specific gravity, 1007–1010; blood in urine once. Phthalein 33 per cent. in two hours. Wassermann negative. Clinical Diagnosis: Arteriosclerosis; chronic interstitial nephritis. Postmortem: Death due to thrombosis of intestinal vessels. Heart 470 gms. Left kidney (upper) 35 gms. Right kidney (lower) 80 gms. See also text. Sclerotic changes superimposed on congenital anomaly. (Museum No. 2632.)

for a nephritis due to arterial aplasia. Rayer noted a relation between size of the renal artery and the kidney supplied, and that in

[21] Cited by Besançon. [22] Ibid. [23] Thèse de Paris, 1889.

the same individual the two arteries as well as the organs supplied differed correspondingly in size; of course, this is known to every morbid anatomist. I am not so sure that Gaucher's allusion to nephritis resulting from primitive alteration of anatomic elements

FIG. 5.—One-half natural size. M. S.; male; colored; aged forty-eight years. Cardiorenal case; gastric symptoms predominated early; later dropsy; dyspnea; systolic murmur. Polyuria; trace of albumin; casts; anemia. Diagnosis: Pernicious anemia; syphilis of liver. Postmortem: Hydropericardium; hydrothorax; ascites; gumma of liver. Heart 418 gms. Arteriosclerosis. Left kidney (upper) fused with adrenal, combined weight 132 gms.; 2 arteries, 2 ureters separate to bladder; upper half hypoplastic and dysplastic; small segment of lower pole is practically normal. Right kidney (lower) 198 gms. Slight dysplasia but organ distinctly hypertrophied. (Museum No. 905.)

refers to defective bloodvessels as the essential basis. Besançon is perfectly clear; to him a subnormal arterial function exerts a deteriorating influence on the kidney, increases its susceptibility to toxic bodies, and may alone determine a primitive interstitial

nephritis. He formulated an accompanying clinical picture. Babes[24] notes that walls of renal arteries may be thicker or thinner than normal and that the musculature is usually hypertrophic. The arterial dysplasia so obvious in some of my specimens is quite

FIG. 6.—One-half natural size. E. D.; female; colored; aged eighty-two years. Had five children; all dead. Disabled by rheumatism. Pain in body and limbs. Edema of legs; ascites; albuminuria; casts; lobar pneumonia; death. Postmortem: Heart 320 gms. Advanced arteriosclerosis. Pneumonia. Left kidney (upper) 110 gms.; hypoplasia and dysplasia; surface but slightly granular. Right kidney (lower) 200 gms. Note absence of normal renal marking; disorderly arrangement of cortex and medulla. Notwithstanding the rather advanced arteriosclerosis neither of these organs is typic of that condition. The larger is clearly hypertrophied, without conspicuous interstitial fibrosis; sections show a degenerative lesion affecting the tubule epithelium with negligible interstitial change; slight glomerular fibrosis. (Museum No. 466.)

characteristic. As stated above my contention is that this is the essential feature; probably all else is secondary. Osteogenesis

[24] Loc. cit.

imperfecta and neurogenesis imperfecta are both fully recognized; why not, as a basis of many anomalies, a defective arteriogenesis? In some instances veins and possibly capillaries are also implicated—defective angiogenesis.

The organ from which was taken the section depicted in Fig. 7 was removed because of recurring attacks of pain; the case, under the care of Prof. Stewart, will be fully reported elsewhere. The anterior aspect of the kidney showed typic appearance of defective nephrogenesis; the artery figured is from within affected side of organ. Observe fragments of elastica in perivascular tissue, irregular

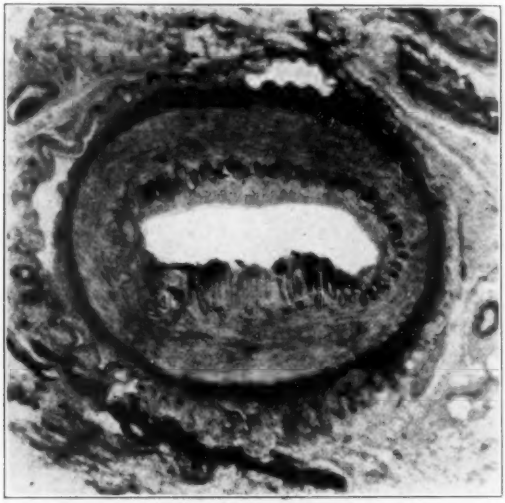

FIG. 7.—Artery supplying involved area of a kidney removed at operation. Fragments of elastica in paravascular tissues; diffuse lime deposit (black) to left and below artery. External elastica almost straight band. Muscle stratum mostly fibrous. Internal elastica atypic, with long sweeping irregular waves notably below. Subintimal proliferation especially marked above. Patient suffered from what was thought to be renal pain or renal angina. Photomicrograph. (Museum No. 2183–B; anterior vessel.)

external elastic lamina of uneven thickness and notably deficient in waviness. The muscle is abnormally thick and contains more fibrous tissue than muscle. The internal elastic lamina is nowhere perfect and below shows long irregular sweeps never seen in normal vessels. Fig. 8 is a smaller vessel from the same organ; the muscle layer is thick, the elastic lamina (but one layer is present) is irregular and imperfect; a considerable arc (lower left) is without elastica; between elastica and endothelium is a fibrohyalin stratum resembling the substance observed by Gull and Sutton. Of course the arteries shown are not normal; were they ever so? I doubt it.

Fig. 9 (section from organ shown in Fig. 1) shows three arteries,

none possessing a lumen proportionate to its size, nor having a normal or vestige of normally distributed elastica; in none is the muscle or intima normal. The organ contained some lime and consequently the section is torn. Below and to the left are groups of hyalin tufts, and a few tubules, two of which are dilated; other tubules containing hyalin are shown near the center. Of course, this patient was old (seventy-three years) and her arteries advancedly sclerotic. The opposite renal artery appeared as sclerotic as those of the small symmetric, miniature or infantile kidney which was

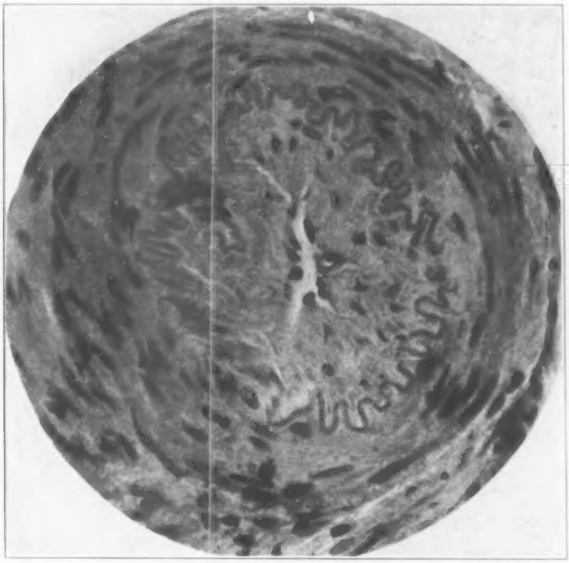

FIG. 8.—Small artery from same case as Fig. 7. Note thick muscle layer; single elastic lamina, imperfect, atypic, and absent from segment below and to the left; break to right; abnormal waviness. Between elastic lamina and slit-like lumen marginated by endothelium note thick fibrohyalin stratum which microchemically gives usual collagen reactions. Arteries from posterior part of this organ did not show these characters or at most but slightly. Photomicrograph. (Museum No. 2183–A; anterior vessel.)

probably hypoplastic at birth or became so shortly afterward; the lesions of arteriosclerosis are superposed. Fig. 10 is of artery from upper pole of organ shown in Fig. 5. The distorted cortex, thickened capsule, irregular surface, unevenly distributed medulla, and abnormal pelvis of upper half of organ shown in Fig. 5, might have been attributed to the associated arteriosclerosis; however, the fused adrenal extending into the kidney substance could have had no such origin. The artery shown in Fig. 10 possesses a single irregular imperfect elastic lamina inside of which is a thick muscle layer; fragmentation of intima seen in many of these vessels is

probably due to contained lime salts. I do not believe that this was ever a normal vessel. In Fig. 11 are two vessels in the midst of a mass of fibrohyalin tissue; the stainable elastica is without its characteristic waves, notwithstanding the fact that obviously both vessels are contracted. To the left is part of another vessel, an artery, with the waveless internal elastica upon which is a thin cellular layer covered by endothelium. Fragments of the external elastic lamina extend into the surrounding fibrous cellular tissue. In the center of the picture is a cellular area; below and to the left several imperfectly developed Malpighian tufts Photograph of section from small kidney is shown in Fig. 6.

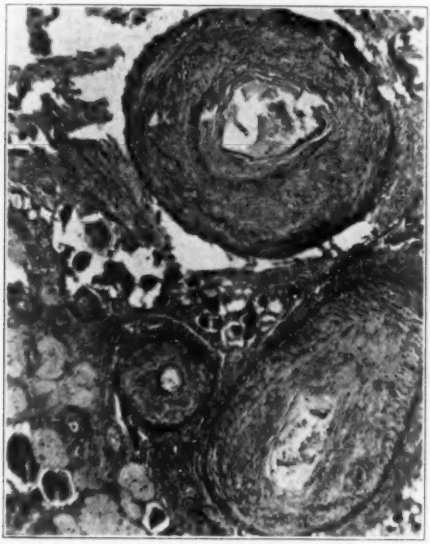

FIG. 9.—Section from kidney shown in Figs. 1 and 2. Three abnormal vessels, apparently arteries. See description in text. Note that normal arrangement of lamina is not present nor are the normal layers recognizable. Below larger vessel note calcified content of degenerated tubules; practical absence of normal epithelium. Below to left many hyalin tufts. Photomicrographs. (Museum No. 1637–8–1.)

The contention is that these kidneys were never perfectly developed, that the arteries were always defective, and that probably the renal hypoplasia rested upon a nutritive basis. Patients may reach an extreme old age without manifesting symptoms, but when anything calls upon the organs for unusual functional activity they break down. Such functional inadequacy is well known in congenital heart disease, in the liver when altered by congenital syphilis, and in allied conditions. Meltzer[25] has shown that in many organs,

[25] Jour. Am. Med. Assn., 1907, xlviii, 655.

notably the kidneys,[26] there is a generously beneficent excess of our actual needs. We may by various morbid processes diminish the abundance perilously close to the danger-point. It is equally certain that the patient may be born without the generous supply usually afforded, or, if adequate at birth, faulty or arrested development of the kidney may later exert a crippling influence. It is in such position that these patients find themselves. They may pass through life with no renal manifestation, and in such cases the

FIG. 10.—Transverse section of artery from upper pole of smaller kidney shown in Fig. 5. Fragments of elastica in paravascular structures; vessel elastica atypic in location and morphology. No muscle external to elastica and abnormally thick fibromuscular stratum between elastica and lumen. Completely detached endothelium. Tissue around vessel is formative in type, contains fibroblasts in varying stages of development. Photomicrograph. (Museum No. 905–3.)

symptomatology which Besançon[27] and also Jianu and Meller[28] and others have attempted to establish, may be absent. Of 9 cases embraced in this study in 3 renal disease was clearly indicated, and in 1 the diagnosis of chronic interstitial nephritis was made with full recognition of associated cardiovascular phenomena; in another the

[26] This phase of renal function is fully discussed by Karsner, Bunker and Grabfield, Jour. Exp. Med., 1915, xxii, 544, who also give references to earlier work.

[27] Loc. cit.

[28] Loc. cit.

diagnosis was chronic nephritis. One of the patients was brought to the accident ward, admitted unconscious with a provisional diagnosis of uremia, and died during transfer to the ward. In this case no doubt a careful study would have resulted in recognition of the condition. One of the patients operated upon (not one of the 3 just mentioned) had been explored and, because the posterior part of the kidney was normal and the anterior alone affected, the condition was not recognized even at operation. The most carefully studied case in the group is the one for which I am indebted to Prof. Stengel.[29] Pregnancy, associated toxemia and eclampsia, with the report that she had had kidney trouble all her life, were

FIG. 11.—Insular fibrosis surrounding small group of imperfectly formed vessels. In center mononuclear infiltration. Below many fibrohyalin glomeruli; others are cellular in centers of dilated tuft spaces. Photomicrograph. (Museum No. 466.)

suggestive; a systolic pressure above 200 mm., and at one observation 230; a trace of albumin; low specific gravity; phthalein elimination 40 per cent. in two hours; non-protein nitrogen 33 to 36 mgs. per 100 c.c. It is probable that ureteral catheterization might have cleared up the case. Besançon[30] lays particular stress upon history of chlorosis or of a chlorotic appearance, headache, vomiting, lassitude, slightly puffy eyelids, slight diffuse edema of lower extremities, frequent micturition, pale abundant urine; obviously none of these alone, nor all together would constitute anything peculiar or characteristic. Nephritis, toxemia, or uremia,

[29] Prof. Stengel was kind enough to permit me to examine the clinical history and make the necessary abstract. I am indebted to Prof. Allen J. Smith and Dr. Fred D. Weidman for the privilege of studying the specimen.

[30] Loc. cit.

coming on in young persons without adequate cause should arouse suspicion. Obviously the Roentgen ray and a careful differential study of excretion from the two ureters would be of distinct aid in diagnosis. By the use of these modern methods Dr. Alexander Randall has recognized the condition and has operated upon a patient having renal abnormality apparently of this type. With well-known functional tests at present at the disposal of the clinician it would seem that the condition should be recognized, and that, with a knowledge of the possibility of such an anomaly, a closer scrutiny of atypic cardiorenal cases should result. Because of operative risk incident to attack upon the better kidney the condition must be of particular interest to the surgeon.

THE RARITY OF CONJUGAL PHTHISIS.

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During fifteen years of service as physician to the United Hebrew Charities of New York City I have had under observation over 800 tuberculous patients annually, most of them married, and a considerable proportion having quite large families. At the beginning of the service, influenced by the current teachings of the dangers of exposure, every consort of a tuberculous patient was suspected of having contracted the disease. The least indication of trouble pointing to the respiratory tract was sufficient to suggest phthisis, and a diagnosis of this disease was made more often than was justified by the subsequent observation of the cases. But with increasing experience among this class of patients I became convinced that tuberculosis in both husband and wife is exceedingly rare, and I drifted to the other extreme—the fact that a woman has a husband with active phthisis would not influence me in interpreting doubtful symptoms and signs in favor of making a diagnosis of this disease because of the exposure to infection to which she has been subjected.

An investigation three years ago[1] showed that the children of these dependent consumptives are infected with tuberculosis to the extent of 84 per cent. when they reach the age of fourteen. The consorts of these tuberculous patients have been found almost invariably "reactors." Bearing in mind that while a positive reaction to tuberculin is conclusive evidence that the person has been infected with tubercle bacilli at some previous period of his or her life, but it by no means shows that the patient is sick as a result

[1] Fishberg, A Study of the Child in the Tuberculous Milieu, Arch. Pediat., 1914, xxxi, 96, 197; 1915, xxxii, 20.

of this infection, it appeared to me rather paradoxical: The children are nearly all infected; the consorts all show conclusive evidences of harboring tubercle bacilli in their bodies, yet phthisis in both husband and wife is so rare as to warrant investigation. Moreover, the children, especially infants living with parents who suffer from active phthisis, are nearly all suffering from some form of tuberculosis, and an enormous proportion succumb, particularly to the meningeal form. Still, the husband of a tuberculous wife, or the wife of a tuberculous husband is only exceptionally affected with the same disease.

This is a fact which is not well known and, in general practice, as well as in the various tuberculosis clinics in this country, the consorts of tuberculous patients are always suspected of being phthisical. It appears that a statistical investigation of this problem may prove of value, and may perhaps stimulate others to collect similar statistics, considering that opportunities for such investigations are abundant in the numerous tuberculosis clinics and sanatoriums in any city of this country.

The tuberculous patients reported on in this paper were mainly dependent people, supported wholly or partly by the United Hebrew Charities. Their dependency was in most cases the result of tuberculosis. At first it was projected that about 500 should be examined, but when it was found that our general impression was fully confirmed when 170 couples were examined, I deemed it safe to report on this number, feeling confident that an increase in the number would not materially alter the result.

Inasmuch as the problem of exposure is most important when speaking of the transmission of tuberculosis, it must be mentioned that these patients were of the same class; in fact, a large number were the very families, which were investigated three years ago as to the incidence of tuberculosis in their offspring. At that time we found that they averaged 3.3 rooms per household, or 1.57 persons per room, the size of which was, in the vast majority of cases, the minimum that can be found in New York City tenements, and many of the sleeping rooms had no windows communicating directly with the external atmosphere. Another way of showing the mode of life of these tuberculous and dependent families is by mentioning that counting all the beds, cribs, couches, etc., it was found that there was only 0.58 of these articles of furniture per person.

We thus find that there were present practically all the factors which favor the dissemination of tuberculosis, and most of the factors predisposing to the development of phthisis, namely, overcrowding in dingy tenements, poverty with its concomitant malnutrition, etc.

Of the 170 consumptives, 9 were women and 161 men. In the latter group we found that 78 of the wives lived with their tuberculous husbands at home, and of these 51 slept in the same room with their sick husbands, and 23 even shared their beds with them.

Of the rest, 27 of the tuberculous husbands were inmates in sanatoriums and hospitals for consumptives and 5 were away from home, though not in institutions. An inquiry was made whether cohabitation has taken place since the onset of the disease in the sick partner, and it was ascertained that 146 acknowledged that such was the case while the rest denied it, though we have good reasons to believe that most of them were not truthful in this respect. We also found that during the time of the illness of the affected consorts, 48 children were born to these couples and two women were pregnant at the time this investigation was made—51 of the women were widows, having lost their husbands through phthisis.

Among the 9 men who had phthisical wives 1 wife was found suffering from active tuberculosis in the advanced stage. But a careful inquiry revealed the fact that she was phthisical before the disease developed in the husband. We have a record of several examinations of this woman for six years back, and she showed symptoms of phthisis until one year ago, while her husband was fairly healthy. At this examination a large dry cavity was found in one of the upper lobes of her lungs, so that if any transmission had taken place it was from the wife to the husband. The other 8 husbands showed no symptoms or signs of tuberculous disease.

Of the 161 wives of tuberculous husbands four were phthisical, though in only one the lesion in the lungs showed signs of activity, while in the other three it was either quiescent or arrested.

It is thus seen that only 2.5 per cent. of the wives of 161 phthiscial husbands were found to be suffering from the same disease, despite the fact that they have been exposed to infection more than women with healthy husbands.

A review of the literature on the subject shows that previous investigations of this character were in most cases in agreement with our results. Soon after Koch's announcement of the discovery of the tubercle bacillus, many of the best clinicians of those days stated that their experience had led them to the conviction that tuberculosis is not a transmissible disease, because it is exceedingly rare to find that a married tuberculous patient should transmit it to the healthy consort. But soon there appeared in medical journals many cases showing that such transmission is not uncommon. Instead of giving detailed histories of such cases we will quote Wilson Fox's[2] summary of the evidence on this point:

"A. One phthisical man married several times, most of his wives becoming phthisical—13 cases.

"B. Consumptive man who died transmitted to wife; widow infected second husband—3 cases.

"C. Man infected wife and died. Widow remarried and also died of phthisis, as did her second husband after he had remarried. His widow lived and also married again, and the next husband died of phthisis.

[2] Diseases of the Lungs, London, 1891, p. 571.

"D. Woman married in succession two phthisical husbands, and became phthisical after the death of the last—2 cases.

"E. Wife consumptive, died, having infected husband, who also infected a second wife—10 cases.

"F. Consumptive wife before dying infected her husband, who later infected a second wife. This widow afterward infected a second husband—1 case.

"G. Woman died of consumption. The widower, not stated to be phthisical, married subsequently three other wives; total four wives, of whom the first, second, and third died of phthisis, but the fourth wife, and apparently the husband, remained free from the disease."

Such cases have been reported by the hundreds in the medical journals of twenty-five years ago. But it must be acknowledged that they are not conclusive proof that phthisis is more frequent among the consorts of the tuberculous than among those who are married to non-tuberculous persons. Single isolated cases of the coexistence of the same disease in both husband and wife may be found in any other pathological processes. We have only to mention *cancer à deux* or conjugal cancer, cases of which have been reported in abundance. But it is the consensus of opinion that in these cases the cancer was not transmitted from one partner to the other. In J. Wolff's[3] great work on cancer, as well as in W. Roger Williams's[4] book on the same subject, we find numerous cases of conjugal cancer which read like the above-mentioned cases of marital phthisis. Similarly, Betz, Oppler, Boisumeau, R. Schmitz, C. Külz, cite details of cases of conjugal diabetes, but an analysis by H. Senator[5] shows conclusively that they do not prove the transmissibility of this disease and that they are merely coincidences.

The only satisfactory way to study the problem of marital phthisis is the statistical. If we find that a large number of consorts of consumptives develop the same disease, we may conclude that it has been transmitted from the sick to the healthy consort.

A careful search of medical literature has revealed the following data about conjugal phthisis:

Austin Flint, Sr.,[6] found only 5 among 700 cases of phthisis in which there was room for the suspicion of the disease having been communicated from the husband to the wife or the wife to the husband. Reginald Thompson[7] found among 25,000, 15 cases of phthisis in both husband and wife, "so that the proportion of infective cases may be reckoned as not less (probably a little more) than one per mille." In his extensive experience Wilson Fox[8] had

[3] Die Lehre von der Krebskrankheit, Berlin, 1914, ii, 58.
[4] The Natural History of Cancer, London, 1908, pp. 194, 262.
[5] Berlin. klin. Wchnschr., 1908, xlv, 133.
[6] On Phthisis, Philadelphia, 1875, p. 419.
[7] Lancet, 1880, ii, 727.
[8] Loc. cit., p. 561.

only met two instances of conjugal phthisis. In one he had only heard that a wife had died of phthisis whose husband, still living, was seen by him five or six years before with a cavity after an acute attack, but he did not know her family history. In the other case the wife died of acute tuberculosis about one year after her husband's death, but she was a member of a family which he knew to be phthisical. When mentioning this fact, he adds significantly, "my experience now extends over twenty-seven years." Leudet's[9] experience was to the same effect: Investigating the subsequent history of 112 widows and widowers whose partner died from tuberculosis he found all alive and not developing any symptoms or signs of phthisis. He concludes that among the well to do classes, who live in comfort, in healthy homes and are well-nourished infection with phthisis is extremely rare.

Sir Hermann Weber[10] collected statistics on this subject. He found in the history of "68 persons, male and female, who with more or less pronounced consumptive taint have married healthy partners. One of the several of the partners of 10 of these 68 cases became consumptive. The question, however," he says, "takes a different aspect if the originally tainted husbands and wives are considered separately. Of the 68 persons, 39 were husbands, 29 wives. Only one of the husbands became diseased, while of the wives 9 out of the 39 husbands became affected. These 9 husbands lost 18 wives, namely, 1 lost 4 wives, 1 lost 3, 4 others lost 2 each, and 3 only 8 each."[11]

An analysis of these figures is not productive of conclusive results on the problem of the transmission of phthisis from husband to wife. It seems that many of these husbands were sufficiently resistant to the disease as to live long enough to fatally infect more than one wife; the wives were, on the other hand, very vulnerable, which would point rather to either a series of coincidences, considering the small number of cases reported, or that they were a select group, studied for the purpose and selected because of the striking features they presented.

Conclusive proof would only be a large number of cases taken at random. Such a series of cases were reported by I. Burney Yeo.[12] He collected particulars of 1055 cases of consumption which had come under his observation consecutively in the hospital. Of this

[9] Gaz. hebd. de méd., Paris, 1890, xxvii, 102.

[10] On the Communication of Consumption from Husband to Wife, Tr. Clin. Soc., London, 1874, vii, 144.

[11] It appears that cases in which a tuberculous husband lost several wives in succession through phthisis are very abundant in medical literature. They appear to confirm Pearson's theory of sexual selection, or "assortative mating" as he calls it, and indicating that persons with phthisical constitutions are attracted by others with the same taint. This point will be discussed later on in this paper. Wilson Fox (loc. cit., p. 572) says: "The group of husbands to many wives would appear to me to point even more strongly to one common cause other than contagion."

[12] Contagiousness of Consumption, Brit. Med. Jour., 1882, i, 895.

number 621 were males and 433 were females. Of the males 306 were married, 297 were single, and 18 were widowers; about 3 per cent. of the whole, and about 6 per cent. of those who had been married. Of the 18 widowers 2 only could state positively that they had lost their wives by consumption and one of these wives had been dead thirteen years; 6 of them had lost near relatives by consumption (father, mother, brother, or sister) giving a presumption in favor of hereditary predisposition, and in 10 no precise information could be obtained. Of the 434 females, 199 were married, 206 were single, and 29 were widows; the widows being about 7 per cent. of the whole, and about 15 per cent. of those who had been married. Of the 29 widows, 5 only were able to state positively that their husbands had died of consumption, 1 lost her husband in a 'fit,' 6 had lost near relatives by phthisis, and 17 could give no precise information.

Yeo also quotes statistics of J. P. Barlett who found that among 94 males in the hospital with phthisis, 53 were married, 37 were single, and 4 were widowers; of these 4, 2 had lost their wives by consumption. Of the 53 whose wives were alive, all the wives, except 2 were quite healthy. Of the 83 females who were then in the hospital with consumption, 62 were single, 15 married, and 6 widows; of the 6 widows 3 had lost their husbands by consumption; in 2 of the 3 there was marked hereditary predisposition; and in 1 there was none; in the remaining cases the husbands were healthy.

"Taking these figures for what they are worth," concludes Yeo, "it seems certain that the communication of consumption from wife to husband, even among the class in which the conditions of life favor to the utmost the communication of contagious disease, is very rare; while it would seem that communication (assuming for the sake of argument, the disease was really communicated) from husband to wife is more frequent."

More recent investigations appear to bear out Yeo's conclusion. Thus of 159 couples in which one of the partners was tuberculous, Brehmer[13] found that in 19 or 12 per cent. both suffered from the same disease. Haupt[14] found in 417 cases 22, or 5.2 per cent., in which both partners were affected with phthisis, which is not above the normal number expected in the average population irrespective of excessive exposure. Only Cornet[15] found among 594 couples that in 23 per cent. of cases both partners were tuberculous which is double that found by Brehmer and he explains the disparity by the fact that his patients were hospital cases, *i. e.*, of the poorer starta of population while those of Brehmer and Haupt were well-to-do private patients.

[13] Therapie der Chron. Lungenschwindsucht, Berlin, 1885
[14] Deutsch. med. Ztschr., 1890, p. 340.
[15] Tuberculosis, American edition, 1904, p. 265.

There are other statistics available on this subject. Ch. Mongour[16] found among 440 married couples in which one of the consorts was sick with phthisis, there were 16 in which the partner was also affected, *i. e.*, 4 per cent. W. Thom[17] found among 402 married couples only 12, or 3 per cent., in which the partners had in all probabilities contracted the disease from their consorts. Meissen found probable infection in 5 per cent. of married tuberculous patients. Jacob and Pannwitz,[18] in a collective investigation in several German sanatoriums admitting patients from all classes of society, that in 8.5 per cent. conjugal phthisis could be found.

An excellent statistical work on this subject was published by Wilhelm Weinberg,[19] who found that among 1426 husbands of tuberculous wives 118, or 8.3 per cent. died from this disease; among 2506 wives of tuberculous husbands 112, or 4.5 per cent., succumbed to this disease. Among a total of 3932 consorts of tuberculous persons, 230, or 5.9 per cent., died from tuberculosis. He thus finds that the mortality from phthisis among those who are married to consumptives, is about double that observed in the general population. Taking the elements of age, sex, etc., into consideration he found that among these 3932 individuals only 2.7 per cent. are expected to succumb to tuberculosis and not 5.9 per cent., as was actually the case. He concludes, therefore, that marriage with tuberculous individuals though not as risky as is generally supposed, yet it is not always harmless. Though he emphasizes that his material shows that not all the tuberculosis thus acquired is due to direct infection from the consort; hardly one-third can be attributed to this cause.

Frier[20] adopted a statistical method similar to that of Weinberg, and found that cancer shows the same double ratio of mortality when its incidence among married couples is calculated according to the theory of probability. After the death of the patients the number of the consorts who succumb to cancer is three times as large during the first year; twice as large during the first five years, etc. Thus the theory of probabilities, as worked out mathematically, yields the same results in cancer as in tuberculosis, which is apparently a confirmation of Pearson's theory of assortative mating spoken of elsewhere in this paper.

Riffel investigated for 200 years backward the demography of a German village with 1200 population. C. Kirchner calculated from his figures that there were 110 tuberculous families among a total of 716, *i. e.*, 15.36 per cent. From these figures it would appear

[16] Recherches statistiques sur la contagiosité de la tuberculose pulmonaire, Congr. internat. de la tuberculose, Paris, 1905, i, 413.

[17] Beitr. zur Frage d. Tuberkulose-ansteckung unter Eheleuten, Ztschrft. f. Tuberk., 1905, vii, 12.

[18] Enstehung und Bekämpfung der Lungentuberkulose, Berlin, 1904.

[19] Lungenschwindsuch beider Ehegatten, Beitr. z. Klin. d. Tuberk., 1906, v, 365.

[20] Quoted from F. Martius, Handbuch der Tuberkulose, Leipzig, 1914, i, 404.

that the wife is more likely to contract the disease from her husband than the reverse which is in agreement with Yeo's and Weber's observations mentioned above. On the other hand Jacob and Pannwitz found that in 142 cases in which the husband was tuberculous before marriage, 133 of the wives remained in good health, and in 24 cases in which the wife was tuberculous before marriage the husband became phthisical in 9 cases. Our figures show that the wife is not excessively liable to contract phthisis because of living with a phthisical husband.

Excellent studies of the risk of infection with tubercle within the family were made by Charles Goring[21] and Pope, Pearson, and Elderton.[22] They calculated the data in the records of the Eugenic Laboratory in England and studied the "degree of resemblance," in this case referring to the presence or absence of tuberculosis in both members of the compared pair, between husband and wife. Inasmuch as their methods of treating statistical figures are above reproach, their results are very interesting and instructive. The net results of their studies were that "there is a much lower 'resemblance' between husband and wife in the matter of tuberculosis than between parent and child, say from 0.25 to 0.30, and yet the intimacy of husband and wife is in most cases a closer one." "The first relation," concludes Karl Pearson, "is precisely that which we find for other characters where the relationship is due to heredity; the second relation is precisely that which we find for other marital resemblances, say insanity. It is therefore difficult to believe it to be due to infection." From extensive and carefully collated statistics Pearson[23] found that as we go downward in the social scale the chances that a tuberculous husband will have a tuberculous wife diminish. This is, however, observed in most other traits of the partners, and has been attributed to sexual selection, or "assortative mating," as Pearson terms it. He found that husband and wife resemble each other in the psychical as well as the physical characters. Common environment can hardly give husband and wife the same eye color, nor the same stature, nor length of cubit—these were determined before marriage. Inasmuch as this selection is largely an intellectual one and has no existence among the poor, it is most prominently observed among the well-to-do and intellectual classes. In other words, Pearson found that phthisical stock is attracted to and mates with phthisical stock. Paul Römer,[24] discussing this problem from another angle, arrives at practically the same conclusion.

The rarity of marital phthisis has been one of the most important stumbling blocks in the teachings of the transmissibility of tuberculosis. We have already mentioned that it was at one time brought

[21] On the Inheritance of the Diatheses of Phthisis and Insanity, London, 1909.
[22] A Second Study of Pulmonary Tuberculosis; Marital Infection, London, 1909.
[23] Tuberculosis, Heredity and Environment, London, 1912.
[24] Beitr. z. Klin. d. Tuberk., 1910, xvii, 383; 1912, xxii, 301.

forward as a strong argument against the infectiousness of this disease, and Karl Pearson, in fact, at present maintains that phthisis is hereditary and not at all transmissible. Cornet,[25] finding that the rarity of conjugal phthisis contradicts his view of infection, argues that "it is incorrect to regard negative instances in the light of evidence against the contagious character of the disease. The error is the result of an exaggerated estimate of the intimacy of the marital relation." In his opinion the wife, and especially the husband, is apt to be kept away from home as much as two-thirds of the day, and that often man and wife meet each other only at night, and even then they frequently occupy separate rooms through disinclination, impotence, age, occupation, or other causes. This, of course, is a wrong view to take especially by one who, like Cornet, is convinced that infection takes place easily in the factory or mill, where fellow workers hardly ever come very near each other, not to speak of breathing closely one near the other, or kissing each other.

The vast majority of the tuberculous patients reported in this paper have not had separate rooms to sleep in; nay, many slept in the same bed with their partners, and children were born to them during the active, *i. e.*, infectious stages of the disease. Yet the percentage of phthisis in both consorts was only 2.5. Of the 51 widows who lost their husbands through tuberculosis from one to twenty years before this investigation was made, only one showed symptoms and signs suggestive of phthisis.

Our figures are in agreement with those recently published by Ludwig Levy.[26] He investigated 317 married couples who lived in poverty and want; 34 per cent. shared the bed, and a large proportion were dependents. After an analysis of his figures he finds that only in 2.8 per cent. was there probable marital infection. He concludes that marital infection is extremely rare, though it is possible, especially among the poorer strata of population.

The rarity of marital phthisis, despite the exposure, is at present explained more satisfactorily than it was formerly by those who saw in it a proof of the non-communicability of the disease, or lack of opportunities to convey the virus, as Cornet stated. Autopsy findings, as well as the tuberculin test, have shown conclusively that nearly all, or at least 95 per cent. of civilized humanity are infected with tubercle bacilli before reaching adolescence. This is a fact which is no longer questioned by those informed on the recent researches on this subject. The fact that tuberculous infection is not in all cases followed by disease of the lungs or other organs is also well established. But it is not generally known that experimental as well as clinical evidence combine to prove that one infection with tubercle bacilli renders the body immune against renewed

[25] Tuberculosis, American edition, 1904, p. 265.

[26] Statistisches über Tuberkulose der Ehegatten, Beitr. z. Klin. d. Tuberk., 1914, xxxii, 147.

infection with the same virus, just as one attack of typhoid, measles, scarlet fever, syphilis, etc., immunizes against these diseases.

It is thus clear that inasmuch as the healthy consorts of tuberculous individuals have already been infected during childhood, they cannot be reinfected by their tuberculous husbands or wives. That they do not develop phthisis is another matter. In adults individual predisposition apparently counts for more than cohabitation with a consumptive consort. Considering that in human tuberculosis, especially in adults, the consumptive is the main source of infection, it is clear that if the wife of a tuberculous husband or the husband of a tuberculous wife, is close to or intimate with her husband, especially sleeping in the same bed, infection should take place, unless the unaffected partner possesses some immunity. We find, in fact, that gonorrhea is transmitted from husband to wife, or the reverse, in a much higher percentage than from 2.5 to 12 which have been found in phthisis. The same is true of syphilis, unless the apparently healthy partner has been immunized by a previous infection.

There is another class of adults who are greatly exposed to tuberculosis, yet escape the disease in a remarkable manner, thus confirming our findings among married people. I refer to the hospital staffs in sanatoriums and hospitals for consumptives. As was shown in another place by the writer,[27] it is extremely rare that physicians, even laryngologists who are very frequently coughed at by tuberculous patients while doing laryngoscopic work, nurses, attendants, etc., should develop phthisis because of association with sources of infection—tuberculous human beings.

On the other hand we have clinical evidence to the effect that when a non-immunized adult person is brought into contact with tubercle bacilli, or with a person who has tuberculosis, he is soon infected with a very severe form of the disease. This is observed when primitive peoples, like the inhabitants of central Africa, Asia, etc., come in contact with civilized human beings, which is equivalent to tuberculized people in the vast majority of cases, they are soon infected with tuberculosis. It has also been observed that when some of these primitive people are brought to large cities in Europe or America they soon contract tuberculosis and succumb to the disease. In fact, the infection being primary in the adult, it almost invariably produces an acute and fatal form of tuberculosis, as is the case with infants among civilized peoples.

It is different with city dwellers in Europe and America. I have observed that in many cases soon after the death of her husband, the widow who nursed him and underwent great privations, often presents vague symptoms and signs of tuberculosis—she is anemic, debilitated, coughs, and at times expectorates sputum containing

[27] Fishberg, Am. Med., 1915, xxi, 607.

tubercle bacilli. But within a few months she recuperates; the cough ceases, she gains in weight and in general health, so that the original diagnosis of tuberculosis is rendered doubtful. Such cases can be observed in any tuberculosis clinics or sanatorium. It is only necessary to note the fact that in the municipal sanatoriums and hospitals for consumptives it is exceedingly rare to find as patients simultaneously or consecutively both husband and wife. Even after the affected consort succumbs to the disease, and the other consort is treated at the clinic for some time for symptoms suggestive of phthisis, which is not rare, the patients does not need admission to the institution. In fact he or she soon recuperates, and is no more in need of medical treatment.

While examining dependent consumptives in Germany, Levy[28] also found similar conditions. It appears that while previous tuberculous infection immunizes an individual against mild reinfections, it occasionally fails when opportunities for massive infection are presented. The superinfection is, however, in these cases only superficial, and the body rids itself of the bacilli soon after the source of repeated superinfections is removed by death or isolation in an institution of the affected consort.

RÉSUMÉ. The simultaneous or consecutive occurrence of phthisis in husband and wife is extremely rare. In an examination of 170 married couples in which one of the consorts was tuberculous, and who lived under conditions favoring the transmission of the disease in poverty and want and under deleterious hygienic and sanitary surroundings, only 5, or 2.9 per cent., were found in which both the husband and wife were affected with the disease.

Many cases in which both the husband and wife are affected with tuberculosis are met with if carefully looked for. But relatively their number is small, and they appear to be coincidences analogous to cases of conjugal diabetes or cancer (*cancer à deux*), of which there are many cases to be found in medical literature. If direct transmission of tuberculous *disease* from husband to wife, or f om wife to husband, was a frequent occurrence, we would meet with conjugal phthisis as often as we meet with gonorrhea, syphilis, scabies, etc., in both consorts. When it is as rare as conjugal diabetes or cancer, we are justified in concluding that the relatively few cases encountered are mere coincidences. In fact, marital phthisis appears to be less frequent than would be expected considering the great frequency of tuberculosis in the general population, especially in the dependent c'asses.

The rarity of conjugal phthisis cannot be considered as a proof against uncontrovertibly proved transmissibility of *tuberculosis* from the sick to the healthy. It is clearly explained by the facts ascertained recently while making autopsies on persons who suc-

[28] Loc. cit.

cumb to non-tuberculous diseases, and while applying the tuberculin test to apparently healthy individuals. These tests have shown conclusively that practically every person living in a large city has been infected with tubercle bacilli during his or her childhood, though not everyone has become sick with the disease as a result of this infection. It has also been found that tuberculous infection immunizes the individual against exogenic reinfection or super infection with the same virus. For these reasons the unaffected consort of a phthisical person, having been infected with tubercle bacilli during childhood, cannot be reinfected through intimate contact with a phthisical partner. Whether the unaffected consort shall develop phthisis depends on entirely other factors.

The bearings of these findings on our practical application of prophylactic measures in tuberculosis are clear.

THE STATUS OF DIPHTHEROIDS WITH SPECIAL REFERENCE TO HODGKIN'S DISEASE.

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(From the Pathological Laboratory, Roosevelt Hospital, New York, 1914–1916.)

At the present time Hodgkin's disease is quite generally believed to be a specific infection, bacterial or protozoan in origin, but for many years it was a debated question whether it was a malignant new growth or a peculiar form of tuberculosis.

In 1884, Weigert[1] demonstrated in glands of this condition organisms resembling the bacillus of tuberculosis, and in 1898 Sternberg[2] published his extensive monograph, treating Hodgkin's disease as a form of tuberculosis. At this time undoubtedly many cases of tuberculosis, lymphosarcoma, and peculiar hyperplasias were described under this heading, for Sternberg wrote "that many cases of so-called Hodgkin's disease, in which by animal experimentation lymphosarcoma had been ruled out, would be of this tuberculous type." This was based on the finding of tubercle bacilli or their results in glands or in some other part of the body in 15 cases with autopsy. Partly confirming this, Reed,[3] in 1902, injected three animals with gland emulsions; one became tuberculous and the other two showed negative findings. Sternberg,[4] in 1905, realized this dual pathology as coincidental. Why these two conditions

[1] Quoted, Fabian: Centralbl. f. allg. Path. u. Path. Anat., 1911, xxii, 145.
[2] Ztschr., f. Heilkunde, 1898, Bd. xx.
[3] Johns Hopkins Hosp. Rep., 1902.
[4] Path. d. Primärerkrankungen d. Lymphat. u. Hämatopoetischen Apparates, 1905.

were so commonly associated at that time is unexplained, for none of the late reports show this complex. In not one of the glands of a series just reported by the author[5] is the picture suggestive of tuberculosis.

Among the early researches on the bacteriology of Hodgkin's disease in this country were those of White and Proscher.[6 7 8] These writers separately and in collaboration demonstrated spirochetes in large numbers in 4 cases of Hodgkin's disease, in 1 case of leukemia, and in 1 of lymphosarcoma. In this latter case a gland emulsion injected into a guinea-pig, caused in two months, at the site of innoculation an ulcer, with enlarged glands in the groin. Spirochetes were demonstrated in large numbers in both these lesions. Staphylococci and streptococci may give rise to a picture simulating Hodgkin's disease histologically, either by direct infection or as an irritative reaction.

Jacobstal,[9] in 1908, found in one case a granular rod not differentiated from the tubercle bacillus. This was injected into a guinea-pig and caused a transitory lymph-gland enlargement. In 1910 Fränkel and Much[10] reported 10 cases of Hodgkin's disease definitely non-tuberculous, in 9 of which they found by the antiformin treatment of glands, a granular rod non-acid fast. The demonstration was made by Much's modification of Gram's stain. In 5 cases of lymphatic leukemia, by the same method, they found a similar organism. Fränkel[11] in a later communication said these rods were very scanty, sometimes a *three days' search being necessary to find them in tissue*. Bunting in his cultural work refers to this point. Hirschfeld,[12] Rosenfeld,[13] Dietrich,[14] Simonds,[15] and Luce[16] have each reported the finding of granular rods in malignant lymphoma in sections, and by the antiformin method. Sticker and Lowenstein[17] have implanted this tissue in pigs and obtained granulomata with and without tubercle bacilli.

Negri and Mieremet,[18] in 1913, published the morphological and cultural characteristics of a diphtheroid organism similar to that described by Fränkel and Much, obtained from the glands of malignant granuloma. In tissue it appeared as a Gram-positive non-acid-fast granular rod 1.3 x 0.8 m., with rounded ends and central constriction. Cultivation on such media as Bordet, Loeffler, and glycerin-phosphate-potato-agar gave the following forms:

1. Short plump rods, 1 x 0.75 m., with many coccoid forms.
2. Small slender rods, 1.5 to 2 x 0.75 m.

[5] Cunningham: Am. Jour. Med. Sc., 1915, cl, 868.
[6] Jour. Am. Med. Assn., August 13, 1907, xlix.
[7] Ibid.
[8] Ibid., p. 1115.
[9] München. med. Wchnschr., 1910, xiii, No. 1035.
[10] Ibid., p. 685.
[11] Ibid., 1911, Part I, lviii, 1266.
[12] Folia Haemat., 1910, Part I, x, 67.
[13] Berl. klin. Wchnschr., 1911, xlviii, 2196.
[14] Folia Haemat., 1912, xiii, 43.
[15] München. med. Wchnschr., lviii, Part I, 1266.
[16] Ibid.
[17] Centralbl. f. Bact., xv, 267.
[18] Ibid., 1913, lxviii, 292.

3. Small rods 2 to 3 m. long with pale granules. These predominated on old Loeffler media.
4. Granular rods, 5 to 7 m. long and 0.75 to 1.5 m. wide.
5. Involution forms.

In large doses these organisms were non-pathogenic to guinea-pigs and caused only a transitory lymph-gland enlargement in the ape (probably irritative hyperplasia). These writers gave it the name corynebacterium granulomatosis maligni.

Bunting and Yates,[19] in 1913, in a preliminary contribution, reported a pure culture of a Gram-positive, non-acid-fast, pleomorphic diphtheroid organism isolated from 4 cases. In later works[20 21 22 23] complete details of the morphological and cultural characteristics and animal innoculation were described. The organism grew well on Dorset's egg media and glycerin-phosphate-agar incubated for about ten days. Old cultures were transformed into a distinct coccus from which the original bacillus was again obtained on favorable media. This point has been considered by them as quite diagnostic of the Corynebacterium granulomatosis maligni. They have obtained it from all active cases. It is non-pathogenic to guinea-pigs and white rats, and at first did not take hold of the ape well, causing only transitory lymph-gland enlargement. They obtained a more virulent strain which caused the death of an ape in ten weeks, and from which the organism was recovered. Three other animals after repeated injections developed regional lymph-gland enlargement. The pathology of these glands resembled Hodgkin's disease in that there was a pronounced endothelial reaction, fibrosis, and sprinkling of eosinophiles, but there was also an extensive necrosis. These writers believe this picture corresponds to the early histology of Hodgkin's disease, the necrosis depending upon the virulence of the organism. According to the writer's experience this is not the picture early or late, and is not seen in the acutely toxic cases. In human histology necrosis is seen, but is rare and occurs only in small isolated foci.

In the literature there is considerable evidence advanced that the Corynebacterium granulomatosis maligni is the established cause of Hodgkin's disease. There is little if any literature describing these organisms as an accidental factor or as contaminations in the cultural work on Hodgkin's disease. The work I have done was an attempt to confirm the findings of others, and in connection with a study of all the cases that have been at the hospital in the last five years, hoping that something might be accomplished by the use of vaccines. Shortly after the onset of these observations a lymph gland was excised which appeared in the gross like Hodgkin's disease. A diphtheroid organism was isolated from this gland which proved

[19] Arch. Int. Med., 1913, xv, 236.
[20] Jour. Am. Med. Assn., 1913, lxi, 1803.
[21] Ibid., 1914, lxii, 516.
[22] Johns Hopkins Hosp. Bull., 1914, xxv, 173.
[23] Ibid., p. 177.

on section to be tuberculous. Several other glands were cultivated, with the results enumerated below.

The work of Harris and Wade[24] has shown that the diphtheroids are widely disseminated and that many diseases were ascribed to these until the specific cause had later been found. Positive cultures to be of value should have control especially in the cultivation of tissues when the chance of contamination is great. The results of my own observations seem to confirm this. Glands that are not properly cared for may easily be contaminated and harbor the organism which "takes a three days' search to find" to recall the quotation of Fränkel and the reference of Bunting.

If Hodgkin's disease has been produced in the ape with certain cultures then there could be little doubt about the corynebacterium. Necrosis is uncommon in Hodgkin's disease and I dare say never the predominating picture; if such occurs other organisms must be associated. Necrosis is seen in the pyogenic infections, syphilis, tuberculosis, and neoplasms. There is also a reaction in lymph glands due to some type of irritation, showing itself as a pronounced endothelioid hyperplasia, in which the diagnosis without full clinical history is difficult. We know from the work of Blumer[25] that glands of status lymphaticus (bacterial-free?) injected into guinea-pigs will cause lymphatic necrosis, and from the work of Woltman[26] similar effects from foreign sera, etc., may be obtained. In this connection, however, we might say that emulsions of any tissue, bacterial-free, could cause such change a sort of anaphylactic reaction. We cannot say, however, that such reactions are not the results of action of the products of bacteria. Herein lies the etiology of the so-called irritative hyperplasia of lymph glands.

The following grouping is made purely on the grounds of technic in the cultivation. In the first group, glands removed in the operating room were brought to the laboratory in a sterile towel. Here after hastily boiling up the instruments used in gross pathological work some of the glands were mashed, others squeezed and planted on tubes of egg, glycerin-potato-agar and Loeffler. The result of this group is as follows:

GROUP I. *Case I.* (A) Caseous tuberculous glands. Cultures were made on blood-agar slants. At the end of forty-eight hours slight cloudiness was noted about the tissue and Gram's stain showed a plump bipolar rod with body of organism staining pink. Colonies were very small and tenacious. With Gabbet's stain the polar bodies were more resistant to acid. The organism remained as a bacillus throughout twelve days' observation.

(B) Glands from the opposite side of the neck two weeks later. In four days from glucose-agar slants a large and small Gram-

[24] Jour. Exper. Med., 1915, xxi, 493.
[25] Quoting Flexner, Johns Hopkins Hosp. Bull., 1903, xiv, 275.
[26] Jour. Exper. Med., 1905, vii, 119.

positive bacillus and coccus were isolated. Transplants gave a good growth of a Gram-positive pleomorphic rod. On Loeffler forms appeared more slender. Morphologically it is different from that isolated from the opposite side of the neck.

Case II. Caseous tuberculous glands. Cultures made on glucose serum agar and blood agar. In six days from serum-glucose-agar a short Gram-positive rod, bipolar, was isolated. Many coccoid forms were seen. Cultures eleven days old presented many clubbed forms. The younger cultures were similar to IA, but the older cultures showed many involution forms. One tube remained sterile.

Case III. Tuberculous lymph gland. Cultures made on ascitic glucose agar. Two tubes gave a pure culture of Staphylococcus albus and one tube a mixed culture of a short Gram-positive bacillus and coccus. It was impossible to isolate the bacillus, but the few seen showed no pleomorphicity.

Case IV. Subleukemic lymphadenosis. Clinically and pathologically this was a very interesting case, but far from a typical Hodgkin's.[27] A gland was removed from the axilla and cultivated by Dr. Warren. A Gram-positive pleomorphic rod was isolated which became coccoid. It was transformed into a bacillus and recognized by Bunting as a typical Bacillus hodgkini. Some of the other organisms isolated are very similar to this strain and have the same tendency to become coccoid, and these from glands definitely tuberculous.

Case V. Hodgkin's disease. Five tubes were innoculated and three gave a large Gram-positive coccus.

(*a*) Egg tube. Diphtheroid bacillus arranged in parallels, Gram-positive with body staining pink. It appeared first as a short bacillus but with subsequent cultivation on Loeffler the forms appeared longer and more slender. It remained as a bacillus throughout three weeks' observation. The young transplants appear very short, with rounded ends, and became distinctly pleomorphic.

(*b*) Glycerin-potato-agar. A short Gram-positive digastric bacillus was obtained. After seventy-two hours many small coccoid forms were seen. It later became contaminated.

Case VI. Large round-cell sarcoma, primary mediastinal. A supraclavicular gland was excised for diagnosis and cultivated on glycerin-potato-agar and egg media. From one tube was obtained a short Gram-positive bipolar rod with central constriction and from another a Gram-positive coccobacillus. On Loeffler the pleomorphicity of the former was better made out and the forms were more slender. After several days' growth many cocci and coccoid forms were seen. Several other tuberculous glands were cultivated and a large coccus was obtained.

[27] Warren: Proc. New York Path. Soc., 1915, xv, No. 142.

While this work was in progress approximately 225 cultures were made in the wards, operating room, and laboratory, and diphtheroids were isolated several times. None, however, came from the operaing-room cultures. One was from a culture taken from the heart's blood in the morgue. Dr. Warren called attention to the fact that there had been several periods at the hospital when diphtheroids were frequent contaminators in blood cultures. One of these periods followed shortly and several cultures after four to five days presented diphtheroids in the broth. We felt that our technic could be improved, so subsequent cultures were made in the Syms operating room carrying out aseptic technic to the minutest detail, with the following results:

GROUP II. Two cases of Hodgkin's disease, one cervical the other axillary; both showed rapid enlargement in the past few months. Glands from both these cases were cultivated on several tubes of egg and glycerin-potato-agar and remained sterile at the end of two months.

Four cases of tuberculosis:

(A) Soft caseous gland; all tubes gave a Staphylococcus pyogenes albus.

(B) Chronic tuberculous lymphadenitis; all tubes sterile at the end of month.

(C) Retroperitoneal gland (tuberculosis of ileum). Pure culture of Bacillus coli in two tubes; one tube remained sterile for three weeks.

(D) Endothelioid tuberculosis. Four tubes remained sterile. One case of chronic cervical lymphadenitis, unclassified, but with a specific history, gave in two tubes a slowly growing streptococcus.

SUMMARY AND CONCLUSIONS. All these organisms may be placed in the diphtheroid group, and only on morphological grounds am I able to say that many of them are of different strains. The organisms which were isolated from glands of Hodgkin's disease, however, are very similar if not identical with those from the tuberculous glands. In Case I, cultures from glands on both sides of the neck, two weeks apart, gave somewhat different organisms, while that described from IA appeared like the organism isolated from Case II. In some instances the diphtheroids were primarily associated with cocci which later overgrew them.

It is reasonable to suppose that glands draining such places as the mouth, throat, and tonsils should harbor such organisms as are commonly found in these portals. With the evidence at hand, however, the occurrence of them in the laboratory, in blood cultures (appearing rather late), in the heart's blood at the morgue, in ascitic fluid, and in a series of gland cultures of questionable technic, and not in a series where technic is definitely controlled, I am led to believe that we are dealing with organisms whose natural habitat is the laboratory. The series is, however, too small to make

a positive statement, but I do not believe the organism heretofore described bears any relation to the cause of Hodgkin's disease.

I wish to acknowledge with thanks the courtesy of the attending staff in supplying me with the material and the suggestions and coöperation of Dr. Warren.

SOME PHYSIOLOGICAL EFFECTS OF VARIOUS ATMOSPHERIC CONDITIONS.[1]

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Atmospheric environment is an interesting and important factor in many medical problems in which no group of physicians is more directly interested than are the members of the American Climatological and Clinical Association, and, moreover, no one in this country has contributed more than they to the advancement of this phase of medical knowledge.

It is for this reason and also as a result of my own recent experience for three years in the work of the New York State Commission on Ventilation that this topic has been chosen for presentation on this occasion.

It is my purpose to approach the subject more from the physiological point of view in the hope that by a consideration of certain fundamental principles a clearer vision may be afforded of the problems involved in the effect which atmospheric conditions exert upon the comfort and efficiency of mankind as well as of the role they may play in the causation, prevention, and treatment of disease.

The respiratory functions of air focussed the attention of physiologists for generations, in fact, until very recent years. Consequently its effect upon the human body was interpreted solely in respiratory terms and rules of hygiene were formulated upon this basis. Withindoors inadequate ventilation was gauged in terms of deficient oxygen or of excess of carbon dioxide, or later of the presence of certain volatile poisons in the air that was breathed. Outdoors the general effect in health and disease produced by variations in climate or of its temporary representative, the weather, was also ascribed solely to their influence upon the air we breathe. To the truthful part of this hypothesis we all pay fitting tribute in the joy of the full deep breath upon a fine, crisp morning.

Under the lead of Pettenkofer[2] the CO_2 content of the air was for

[1] President's address at the meeting of the American Climatological and Clinical Association, Washington, May 9 to 11, 1916.

[2] Liebig's Annalen, 1862–1863, Suppl., ii, 1.

many years taken as the indicator of hygienic fitness until Haldane[3] showed that the alveolar CO_2 content of the air does not vary even when it is largely in excess of the atmospheric air, and he and others have demonstrated the lack of discomfort or other symptoms until the percentage of CO_2 reaches a point many times in excess of the range of possibility under any but experimental conditions. The same may be said of the effect of diminution of oxygen within any ordinary or probable limits.

In 1887 the researches of Brown-Séquard[4] claiming the existence of volatile organic poisons in expired air and explaining the symptoms of exposure to vitiated air upon this basis claimed wide attention. Although very recently Rosenau and Amoss[5] have reported the presence in expired air of substances which cause an anaphylactic reaction in animals no other observers have been able to corroborate the results or conclusions of Brown-Séquard.

Other substances in the air, such as dust, bacteria, and odors, are recognized as playing a part in its hygienic properties, but recent investigations appear to demonstrate that under ordinary conditions they are not factors of sufficient importance to materially affect health.

In general it may be accepted that the chemical or bacterial content of the air within any likely degree of variation is not of material moment either hygienically or physiologically.

The retention of CO_2 determinations as a gauge of the amount of air change in indoor conditions is the only remnant of the era of chemical standards for determining the hygienic condition of the air, and this gauge so used has no reference to the CO_2 content itself as an important physiological factor.

Researches of the last decade have all led to the appreciation of the physical as opposed to the chemical features of the air as the important physiological factors. It is the reaction of the body to its environment through the skin surface rather than through the respiratory organs which is now recognized as of fundamental physiological importance. This may be expressed as the ventilating function of the skin, and the problems involved are largely those of the satisfactory heat regulation of the body.

Hermans[6] in 1883 was the first to call attention to this important fact, but it was brilliant experiments of Paul[7] in Flugge's laboratory in 1905 that first riveted the attention of the scientific world upon this aspect of the problem. In cabinet experiments he adequately explained all of the symptoms caused by vitiated atmosphere in terms of temperature, humidity, and air movement. Since then

[3] Haldane, Jour. Path. and Bacteriol., 1893, I, 168, 318.
[4] Compt. rend. Soc. de biol., 1887, s. 8, lv, 814.
[5] Jour. Med. Research, 1911, xxv, 35.
[6] Arch. f. Hyg., 1883, i, 5.
[7] Ztschr. f. Hyg. u. Infectious-krankh., 1905, v, 405.

his results have been amply confirmed, notably by Rubner,[8] Flugge,[9] Haldane[10], Leonard Hill.[11]

Adequate heat regulation of the body depends largely upon the capacity for proper heat elimination, which is accomplished in three principal ways, which vary in their relative importance according to the varying external conditions.

1. Evaporation of water from lung and skin surfaces.
2. Direct conduction by contact with a cooler medium.
3. Direct radiation to a cooler distant surface.

1. Evaporation. This takes place continuously from lung surfaces, to a greater or less extent from skin surfaces. Its rate depends upon (*a*) air temperature, (*b*) humidity, and (*c*) velocity of air movement.

Temperature and air movement are of primary importance in skin evaporation and of only minor importance for the lungs. Humidity affects both kinds of evaporation, but in the skin it is the relative humidity which is of primary importance while in the lungs it is the actual amount of moisture that determines the rate of evaporation.

2. Direct Conduction. In contact with the surrounding air the rate of heat elimination from the skin by conduction depends upon the following properties of the air: (*a*) temperature, (*b*) thermal capacity, (*c*) thermal conductivity, and (*d*) velocity of movement.

The thermal capacity and conductivity depend upon (*a*) the density (pressure), (*b*) the humidity, and (*c*) the temperature.

3. Direct Radiation. This is a factor of minor importance, but may heed recognition in the association with the other two more important conditions.

Taking, therefore, these more important conditions together, that is, evaporation and conduction, we find that the various factors reduce themselves finally to four: namely, temperature, humidity, barometric pressure, and velocity of air movement. The interrelationships of these factors are very complex, so that no simple statement of the exact physiological effect of each is possible. For example, it is a well-known experience that high temperature with low humidity is often more comfortable than lower ones with high humidities. Here the effect of humidity upon evaporation is the predominating factor. On the other hand, low temperature with low humidity may be quite bearable, while a higher temperature associated with dampness may be distinctly chilling. Here it is the relation of the humidity to direct conduction that predominates.

In the consideration of the concrete physiological problems which I now propose the factors of the temperature, humidity, and

[8] Arch. f. Hyg., 1897, xxiv, 1.
[9] Ztschr. f. Hyg., 1905, xlix, 363.
[10] Jour. Path. and Bacteriol., 1893, i, 168, 318.
[11] Smithsonian Miscellaneous Collections, 1913, lx, No. 23.

movement of the air will be those mainly considered as the additional factor of barometric pressure will lead us a little too far afield.

EFFECT UPON COMFORT. Analysis of much that has been said and written of the physical effects of air conditions, both within-doors and outdoors, reveals the fact that the opinions expressed are very largely based upon sensation of comfort or discomfort, these are nothing more or less than personal impressions and lack scientific definiteness.

In extreme conditions of heat, humidity, and air stagnation there of course results certain definite symptoms, easily recognizable, and, within certain limits, common to all animal life. A sense of oppression, headache, dizziness, faintness, and nausea are symptoms with which we are all familiar. The fundamental experiments of Paul and others already cited were based upon the causation and relief of such symptoms under varying atmospheric conditions of a physical nature. Such effects are not debatable. When, however, we consider the less extreme conditions the situation is different. There are no definite concrete symptoms, and impressions are very variable.

Haldane,[12] who has done some of the most exact work in this field, concludes, from numerous experiments, that the combination of temperature and humidity records, as shown by the wet bulb thermometer, is the only reliable index, and places the maximum comfort for men at 68 wet bulb while actual symptoms occur at 78 wet bulb.

Professor Afflick[13] in studies of gymnasium ventilation found that 55° to 63° F. dry was never uncomfortable, but that when humidity was considered the individual variations were so great that definite conclusions were not possible. He found that opinions of comfort varied all the way from 29 per cent. to 77 per cent. relative humidity.

Hickor[14] also in studies of gymnasium ventilation found very great variation, but concluded that 58° to 64° (dry bulb) is the best for gymnasium comfort and that variations between 22 per cent. and 65 per cent. relative humidity had no effect on comfort.

The New York State Ventilation Commission[15] found in its cabinet experiments that the subjects were somewhat more comfortable at a temperature of 68° F., but the difference experienced between this and much lower or much higher temperature was not as marked as would have been expected. The same results held good in varying degrees of humidity. One interesting finding was a decrease of appetite in stagnant air and compared with the free admission of fresh air.

In its schoolroom experiments with recirculated air there was no marked difference in the comfort votes of teachers and other obser-

[12] Jour. Hyg., 1905, v, 494.
[13] Am. Physical Educ. Review, 1912, xvii.
[14] Thesis, Internat. Y. M. C. A. College, Springfield, Mass., 1914.
[15] Preliminary Report, Am. Public Health Jour., 1915.

vers between these two conditions, which coincides with the observations of Bass[16] in Minneapolis.

There is a noticable lack of data in the literature as to the comfort effects of low temperature combined with varying degrees of humidity and air movement. It is generally recognized, however, that this is susceptible to personal idiosyncrasies, as many or more than at the higher temperatures, and experience in inuring patients to cold air, often at first strongly contrary to their sensation of comfort, demonstrates how large a role habit plays in this matter.

Many observers have noted also that feelings of comfort often depend upon contrasts. On a cold day a room at 50° F. might seem warm and comfortable while in warmer weather the same temperature might well be uncomfortably chilly, all of which shows our powers of adaptation, but does not increase our confidence in comfort sensation as an index of physical condition. At present, however, they constitute the basis of much of our medical opinion and clinical advice in these matters.

Effect Upon Physical Efficiency. Some evidence is at hand concerning the effect of high temperature and humidity upon working efficiency. Very little exists regarding the similar effects of low temperatures and humidities. Haldane[17] found that when at work, subjects were unaffected at 71° to 72° F. dry, or 64° to 65° wet bulb, but that actual disabling symptoms occurred at 78° wet bulb or above. His observations coincide with others and may be accepted as a present standard.

In the Ventilation Commission experiments it was found that body temperature and pulse rate were raised at 86°, but lowered at 68° and below, and the Crampton index of vasomotor tone was lowered by temperatures of 77° and 86°, especially when associated with high humidities. Systolic blood-pressure was somewhat higher in the lower temperatures. Also 37 per cent. more work in dumb-bell lifting was accomplished at 68° with 55 per cent. humidity than at temperature of 77° and 86° and somewhat higher humidities. In another series 15 per cent. more physical work was done at 68 and 50 per cent. than at 75° F. with the same humidity.

These results with only moderately high temperatures are interesting and of more practical value than the majority of similar experimentd in which very high temperatures are employed, showing, as they do, that degrees of moderate heat which are often experienced under ordinary conditions of life are not without measurable physiological effect.

Efforts to obtain more exact physiological indices of the response to temperature than the usual ones employed of body temperature,

[16] Am. Soc. Heat. and Vent. Engineers, 1913, xxix, 328; ibid., 1915, xxi, 109.
[17] Jour. Hyg., 1905, v, 494.

pulse rate and blood-pressure, were made. Studies with this end in view were made by Professor Frederic S. Lee upon the duration of digestion, the alveolar CO_2, the oxyhemoglobin in the blood, the rate of pulse recovery, the size of the dead space in the lung, the specific gravity and freezing-point of the urine, and the excretion of creatinin, but all failed to show any definite changes as a result of various atmospheric conditions.

One of the most interesting contributions to this general subject is Ellsworth Huntington's[18] recent book. In support of his main thesis, namely, that conditions of weather and of climate play a dominating part in the development of peoples as well as of individuals, in those characteristics which go to make up the general sum of what we call civilization, this interesting writer makes use of carefully controlled observations and statistics upon the working efficiency of several large groups of workmen under various conditions.

The groups observed in these studies were operators in three factories in Connecticut, Bridgeport, New Haven, and New Britain respectively, girls in a tobacco factory in Winston-Salem, North Carolina; operators in two cotton mills in South Carolina and in two others in Georgia; a group of cigarmakers in Jacksonville and another in Tampa, Florida, and, lastly, carpenters in Jacksonville, Florida.

From all of these diverse sources he obtains remarkably harmonious results and reaches conclusions which may be summarized as follows:

1. There exists a regular seasonal variation in physical efficiency which in this climate is shown by two maximum waves, one occurring in the spring, May and early June, and the other in the autumn, October and early November, with a corresponding depression in midwinter and midsummer.

2. The main factor in the seasonal variation is temperature. The percentage of sunshine and relative humidity are minor factors of some, but relatively slight importance.

3. Extremes of temperature whether high or low are detrimental, and there exists an optimum temperature for physical efficiency, which Huntington's statistics shows to be 60° F.

4. A change of temperature, if not too great, is more stimulating to working efficiency than uniformity, and a fall of temperature has more effect than a rise. A fall of 4° to 7° F. is everywhere stimulating.

5. Efficiency is more marked at the end of a storm and least so on very clear days. Each storm with its changing skies, varying humidities, and slow rise and rapid fall of temperature is a stimulant and raises efficiency.

[18] Civilization and Climate, New Haven, 1915.

6. The ideal climate from the stand-point of efficiency is one in which the temperature range is between 38° and 65° F., in which the humidity is uniformly neither very high nor very low, and in which there occur frequent but moderate variations in temperature from day to day, interspersed with a considerable number of cyclonic storms.

These opinions which I have thus briefly summarized when supported by the data and reasoning which Professor Huntington presents, deserve careful thought and critical study at the hands of the clinicians and especially of climatologists.

EFFECTS UPON MENTAL EFFICIENCY. Of the influence of atmospheric conditions upon effective mental effort much has been claimed from time to time, but little has been proved.

Lehmann and Pederson[19] conducted a long series of experiments upon school children which included addition and memory tests as well as strength tests with the dynometer. They found a seasonal variation in both the mental and physical tests very similar to those of Huntington, with an optimum temperature for both mental and physical efficiency which varied greatly between individuals. In general the optimum for mental work was found to be much lower than that for muscular exertion.

Huntington[20] made careful observations of the relation between mental efficiency and weather and seasonal changes, as evidenced by the study marks of cadets at West Point and Annapolis over several years. He found a seasonal variation of mental efficieney, evidenced by two maximum waves each year. These waves occurred in March and in November or early December, that is, at seasons when the temperature was dictinctly lower than he found to be desirable for maximum physical efficiency.

He concludes that a temperature of about 40° F. is the optimum for mental effort.

Very extensive experimental studies of mental work in various atmospheric environments have been made by the New York State Ventilation Commission. The results of these are soon to be reported by Professor E. L. Thorndike of the commission. In general, however, they showed very little effect that could be demonstrated by the most scientific psychological methods of investigation. The most striking result was a lack of inclination for mental work in high temperature, such as 86° F. with high humidity (80 per cent. rel.), but even here this could be overcome by the application of some increased incentive to work.

General experience with outdoor schools leads to the impression that conditions there make for increased mental capacity. If this be true, as seems likely, it would be a rational explanation to ascribe this benefit to the much lower temperatures which obtain in these class

[19] Arch. f. d. ges. Psychol., 1907, x, 1. [20] Loc. cit., p. 77.

rooms. With the large number of outdoor schools there now exists so much available material for statistical investigation that it is to be hoped that some well-conducted and carefully controlled studies of this subject will be forthcoming. It would be specially interesting and instructive to know more of the actual effects of the very low temperatures often noted in these classes, for they are far below the optimum temperature for mental work suggested by Huntington and by Lehmann and Pederson.

Clinical Features. There are many interesting and important applications for the physiological problem which we have thus briefly considered. At the present time I will attempt to discuss only two of the more important of these, namely, "Ventilation" and the "Fresh Air Treatment" of disease. The first concerns us chiefly in the conservation of health and the prevention of disease, while the latter is a generally accepted and invaluable therapeutic agent.

If we are to adapt the knowledge obtained from physiological research to these practical problems it is evident that the chief emphasis is to be placed upon atmospheric temperature.

Our standards have been largely those of individual comfort which we have seen to be susceptible to very considerable variation and to depend very largely upon the facility of adaptation to the body environment.

There has been a considerable amount of loose medical thinking upon this subject and we are sorely in need of more scientific data based upon accurately observed clinical phenomena. Fully as I appreciate their shortcomings, I am not entirely in sympathy with the popular denunciations of ventilating engineers and their artificial systems.

The fault appears to me to be more one of our standards, for I I am convinced that by a rational combination of open windows, a good heating plant, and a proper air exhaust system when necessary that practically any desired condition of indoor air may be obtained. The two chief faults appear to be too high temperature and too little variation in temperature.

The results of recent studies all appear to point in this direction, and were we able to agree upon new standards embodying the correction of these faults there is little doubt of the availability of the physical means to carry them out. Any system of ventilation, however, whether natural or artificial, stands or falls by the intelligence with which it is operated, which presupposes a knowledge of the desired ends to be obtained. There would seem to be needed, therefore, a wider appreciation of the physiological importance of cooler and more variable temperatures as the prime factors in proper ventilation to which all others, including even humidity, are secondary.

When we turn to the fresh air treatment of disease it would seem as though here also we have much to learn from physiological studies. If there is advantage to be desired from open air, as it

happens to be, it would seem as though there might be still more to be gained from skilful modification of these air conditions to meet the indications arising in various diseases or in individual cases. This would involve not only a more general knowledge of what is known of the physiological effects of various atmospheric conditions, but, what is even more needed, a systematic attempt to extend this knowledge by a correlation of the physical, physiological, and clinical factors involved. This can come only through close study of the reaction of various types of disease to the atmospheric environment, and entails the use of accurate records of temperature, humidity, barometric pressure, and air movement as a part of regular clinical procedure.

It would seem, for example, that valuable use might be made of Huntington's suggestion of the effects of temperature change when the weather does not happen to supply it adequately or that the ill effects of certain seasons or weathers might be modified and the good effects of others artificially reproduced by the intelligent use of means easily at our command.

The great variation in medical opinion upon these matters demonstrates the fact that our clinical knowledge is still imperfect and inexact and that standards of procedure in various diseased conditions must be supplied by careful clinical study and experimentation.

My suggestion, therefore, is that by breaking up into its component parts the heterogeneous mass of physical and physiological factors, now included in the term "Fresh Air Treatment," and studying the effect of each, we may be able to reach a point where the proper atmospheric conditions may be intelligently applied to the suitable case of disease, and results obtained which would be far more satisfactory than at present, both from a clinical and scientific point of view.

I believe that we can confidently look to the members of the Climatological and Clinical Association to take the lead in this direction.

OBSERVATIONS UPON A CASE OF EXTREME ACIDOSIS OCCURRING IN A MAN WITH BILATERAL CYSTIC KIDNEYS.

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We have recently had an opportunity to make observations of the various factors of acidosis in a case of bilateral cystic kidneys

with terminal uremia and accompanied by extreme dyspnea. These findings seemed sufficiently remarkable to us to be worthy of recording.[1]

The clinical history was as follows:

S. C., male, aged forty-six years; single; colored; bricklayer. Hospital numbers 207051, 207864, 208858; entered the medical service of the hospital February 29, 1916.

Family History. Unimportant.

Past History. Typhoid fever eight years ago; gonorrhea three times, the last ten years ago. No history of syphilis.

Habits. Good. No alcohol or tobacco. Bowels always very constipated.

Present Illness. During the last five years, for about two months in the middle of each winter, he has been bothered with certain gastro-intestinal symptoms, flatulence, abdominal distress, vomiting, anorexia, and loss of weight and strength. With these symptoms he has in addition occasionally had some edema of the face, hands, and feet and a moderate polyuria. He was sent to the hospital from the out-patient department in order that a lumbar puncture might be done. In the out-patient department bismuth roentgen rays had been taken which showed nothing abnormal save a rather active hypertonic stomach and some delay in the passage of the bismuth mass in the lower portion of the descending colon.

Physical Examination was essentially negative. Pulse, temperature, and respiration were normal. The blood-pressure was 135 mms. systolic and 70 mms. diastolic.

Laboratory Examinations. The urine showed the slightest possible trace of albumin; in other respects it was normal. No casts were found. The blood: Hemoglobin 80 per cent., white count 7200; the smear was not remarkable. The Wassermann test was negative. The spinal fluid was clear; there was no excess of cells; the gold chloride and Wassermann tests were negative.

The patient was discharged March 1, 1916. He entered the hospital again April 17, 1916, having failed to improve; he came in for further study on the advice of his own physician. He remained in the medical wards until May 16, and during that time he developed and recovered from an unexplained fever of twelve days' duration.

Physical examination at this second entry showed him much emaciated. A systolic murmur was heard over the apex of the heart; a mass was felt in the right upper quadrant of the abdomen which was thought to be kidney. It was felt by several observers. There was no edema.

The urine was examined repeatedly during this stay in the hospital and was always of low specific gravity, sometimes showing

[1] We are indebted to Dr. W. H. Smith for the opportunity to study this case.

a slight trace of albumin, sometimes none. No casts were ever found. The blood even at the height of his febrile attack showed no leukocytosis.

The blood-pressure was never higher than 135 mms. systolic, and at the height of his febrile attack was only 100 mms.

The renal function (sulphonephenolphthalein excretion) was determined on several occasions. On April 1 it was less than 5 per cent. in two hours. It was the same on April 25, and on May 4 only a trace was eliminated in two hours.

The non-protein nitrogen of the blood was 97 mgms. per 100 c.c. April 20 and 71 mgms. May 4.

May 16 he was discharged, slightly improved. The diagnosis was in doubt. It was thought he must be in chronic uremia, and amyloid or cystic disease of the kidneys was thought more likely than a real nephritis. The occurrence of fever and the fact that the patient stated he had previously had fever with his attacks suggested a possible etiology for amyloid disease.

June 9, 1916, he again entered the hospital, this time on the surgical side, with a septic hand which he had had for two weeks. After leaving the hospital the last time he had felt better until the sepsis had begun.

His hand was poulticed and things were going along smoothly until suddenly, on the morning of June 12, he began to have a most extraordinary hyperpnea. He was seen by members of the medical staff in consultation and was transferred to the medical service. At this time, noon, June 12, he gave the impression of a man who has just done the most violent muscular work. Each respiration was maximal and all the accessory muscles were working. The rate was about 25. The patient was perfectly conscious, and stated that he felt as though he had been running. There was no orthopnea and no Cheyne-Stokes periodicity to the breathing. A number of special tests were made at this time which will be discussed later. These showed that an extreme acidosis was present.

The hyperpnea continued during the day, and in the evening the administration of alkali was begun. Sodium bicarbonate, 10 grams every four hours by rectum, was given until 2 A.M., June 14. After that 20 grams was given by stomach tube every eight hours. This was continued until death.

On the morning of June 13 the breathing was still labored, but not nearly so much so as on the day before. The rate was 20; during the extreme hyperpnea it reached 50. The patient was semicomatose. He passed very little urine, and that only after catheterization.

June 14 he was a little brighter. He would answer questions. His speech was thick but not aphasic. There was much less hyperpnea. The accessory muscles were not employed. This day the general character of the breathing was deep and sighing, much like

that of diabetic coma. The rate was 18. In the afternoon he gradually lapsed again into coma. His mouth became very dry. The temperature rose rapidly to 105°. He developed twitchings of the muscles about the mouth. The respirations became gradually less and less stertorous, the rate falling to 10, then 8, then 3, etc., finally ceasing altogether at 11.05 P.M., June 14. The cardiac action was good up to the time the breathing stopped, and continued several minutes thereafter. It was clearly a death from respiratory, not circulatory, failure. A blood culture showed a terminal streptococcus septicemia.

The urine failed to show any diacetic acid or acetone at any time. A slight trace of albumin was present, but no casts were found.

The blood-pressure as before was 135 mms. systolic, 70 mms. diastolic.

AUTOPSY. The kidneys were about three times the normal size, the right being slightly greater than the left. The left kidney substance was practically replaced by mutiple cysts varying in size from that of a pea to about 2 cms. in diameter, and containing fluid varying from a clear, watery substance to light brown, dark brown to black, thick material. The contents of the cysts gave a foul odor. They were not connected with the renal pelvis, which was atrophic, as was also the ureter.

The right kidney showed similar cysts, but smaller and fewer in number. There were small islands of renal tissue between the cysts, but the color was pale and the consistency increased. This renal pelvis was slightly atrophic.

The right lobe of the liver at the rounded, thickened portion showed a few subcapsular cysts containing clear fluid, and deep in the tissue in this region were several cysts, varying in size up to 1.5 cms.

The lungs showed pneumonia at the bases and the right lung showed consolidation extending well up on the posterior surface.

The autopsy (including the head) in other respects showed nothing noteworthy.

SPECIAL STUDIES. This case presented an unusual opportunity for study, so the following investigations were carried out:

Respiration Experiment. June 12, at noon, at the height of the hyperpnea and before any alkali had been given, a five-minute period on the Benedict apparatus (mouthpiece, spirometer type) was secured. This experiment gave these results:

Respiration rate	22.5	
Volume per respiration	2440.0	c.c.
Total ventilation per minute	55.0	liters
Total ventilation per minute reduced to 0° and 760 mms.	50.6	liters
CO_2 in expired air	0.71	per cent.
CO_2 eliminated per minute	360.0	c.c.
O_2 eliminated per minute not obtained		

Alveolar carbon dioxide tension was determined June 12, just before the respiration experiment, by the Plesch-Higgens method. It was 0.9 per cent. or 6.4 mms. of mercury.

The index of urea excretion was determined by the routine described by McLean[2] on the afternoon of June 12 (before any alkali had been given). The diet for the preceding forty-eight hours had been free from meat, fish, and salt. The following data were obtained:

Urea in the blood	332.0	mgms. per 100 c.c.
Urea in the urine	0.449	gm. in 72 minutes.
Volume of urine	55.0	c.c. in 72 minutes.
Patient's weight	60.0	kg.
Index of urea excretion[3]	34.8	

The same urine showed NH_3 0.0104 gms. in seventy-two minutes, or 0.208 gms. in twenty-four hours. No diacetic acid or acetone.

The Alkali Tolerance. The urine remained acid to litmus up until death in spite of the administration of large amounts of sodium bicarbonate as outlined in the history. (Total 110 grams in two days.)

The carbon dioxide capacity of the plasma was determined on several occasions by the method of Van Slyke. At 3.16 P.M., June 12, before alkali administration had been begun the volume of CO_2 bound by 100 c.c. of plasma was 12.1 c.c., equivalent to an alveolar air CO_2 tension of 8.35 mms., Hg.

June 13, at 12.30 P.M., after the patient had been on sodium bicarbonate 10 gms. every four hours for eighteen hours, it was 20.1 c.c., equivalent to a tension of 13.87 mms. Hg. June 14, at 11 A.M., it was 37.4 c.c., or 25.8 mms. Hg.

The renal function (sulphonephenolphthalein elimination) June 12 was zero in three hours.

The acid ammonia ratio, which was determined for us by Dr. W. W. Palmer by the method described by Palmer and Henderson[4] was 1.00. This, Dr. Palmer writes, is to be considered a high normal. The urine for this test was obtained June 12 before any alkali had been given.

The non-protein nitrogen of the blood (Folin method) was 189 mgms. per 100 c.c. June 12.

The blood-sugar (Benedict's method) on June 12 was 0.22 per cent.

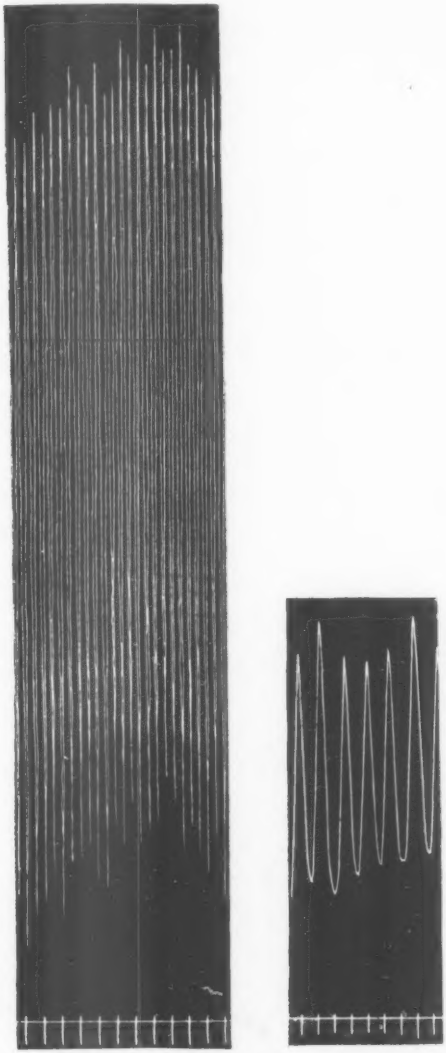
The phosphorous content of the serum Dr. John Howland was good enough to determine for us. Dr. Howland writes: "The

[2] Jour. Am. Med. Assn., 1916, lxvi, 415.

[3] Index of Urea Excretion =

$$\frac{\text{Grams urea in 24 hrs.} \times \sqrt{\text{grams urea per liter urine}} \times 8.96}{\text{Weight in kilo} \times (\text{grams urea per liter of blood})^2}$$

[4] Arch. Int. Med., 1915, xvi, 109.



The patient's respiratory curve, June 12, at the height of the hyperpnea on the left. That of a normal man of approximately the same weight on the right. Both tracings taken with the Benedict apparatus. The time intervals are five seconds. Both subjects lay flat on the back while breathing into the apparatus. A mouth-piece was used in each case.

phosphorus content of the serum . . . . in the form of inorganic phosphates was 18 mgm. per 100 c.c. The normal varies between 1 and 3.5; you see, therefore, the very great excess. This is nearly as high as we have ever found it; up to the present time (June 19, 1916) 23 mgm. per 100 c.c. has been the highest."

The calcium content of the blood Dr. Howland also kindly determined, and writes as follows: "The calcium content of the patient's blood that you were good enough to send me was 3 mgms. per 100 c.c. This is less than one-third the normal, the normals running from 10 to 11. This diminution of the calcium we have found to be almost as regular as the increase of phosphate."

Discussion. This case is interesting in that it presents one of the most intense acidoses ever reported in uremia. Peabody reports one case of uremia having a CO_2 tension (Plesch Higgens) of 6 mms., and another with a tension of 19.1 mms.[5] As a rule, however, in uremia the CO_2 tension rarely falls below 25 mms. even in the terminal stages. Of course, in diabetes CO_2 tension of 6 mms. or less are not uncommon.

The severity of the hyperpnea is extraordinary. The minute volume of 50 liters is easily ten times the normal resting ventilation, and the volume per respiration of 2440 c.c. is at least 60 per cent. of his probable vital capacity, whereas the normal resting tidal respiration is about 5 per cent. of the vital capacity. This ventilation is greater than that of one of us (J. H. M.), who is about the same size as the patient, when he was doing about 800 kg. meters of work per minute on a bicycle ergometer.[6] Under these circumstances the normal subjects CO_2 elimination was over a liter a minute instead of 360 c.c., as in the case of this patient.

That the hyperpnea was in large part due to the acidosis seems probable because of the distinct improvement secured by giving alkali. This improvement was in the respiration only. Although the acidosis was diminished by giving alkali, as proved by the rise in blood CO_2, the patient's general condition grew progressively worse.

That the acidosis was one of retention rather than of production is suggested by low renal function tests, and the low index of urea excretion together with the high phosphates and non-protein nitrogen of the blood and the autopsy finding of almost total absence of normal renal tissue.

That there had been a tremendous withdrawal of base from the body is shown by the high alkali tolerance. In this connection it is interesting to note a striking difference between this case and the cases of chronic glomerular nephritis studied by Palmer, in that here the utilization of NH_3 to neutralize acid, as shown by the acid

[5] Arch. Int. Med., 1915, xvi, 955.

[6] Means and Newburgh: Jour. Pharmacol., and Exper. Therap., 1915, vii, 449.

ammonia ratio, is normal, whereas often in chronic nephritis there is a definite inability to utilize ammonia.[7]

The fact that a severe acidosis is present, that the acid ammonia ratio is normal, and that nevertheless the total NH_3 excretion is not increased shows very clearly that the excretion of acid is greatly impaired.

The clinical picture is similar to that commonly found in bilateral cystic disease of the kidneys. Pain and digestive symptoms are common at the onset. Edema is rare. Terminal uremia is usual. The urine is usually increased in amount, with little or no albumin, low gravity, and no casts. The blood-pressure often shows no elevation.

THE INVASIVE QUALITY OF THE STREPTOCOCCI IN THE LIVING ANIMAL.[1]

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Invasion, virulence, and pathogenicity as well as resistance and susceptibility are all relative terms and must be considered from the point of view of the animal body as well as the bacteria themselves. This is generally recognized but is not constantly remembered.

The streptococci have primarily high invasive powers. By this I mean that they are capable of entering the animal body under a wide variety of conditions. It is only within the last few years that this has been broadly recognized. The Bacillus coli formerly was the organism found as the chief secondary invader. In autopsy bacteriology the colon bacillus is frequently reported as the common bacterium invading after death, and in studies of peritoneal and other fluids the same organism was found practically to the exclusion of all others. More careful technic has, however, definitely shown that streptococci of various types invade the tissues and body fluids long before the colon bacillus, and are, moreover, almost always present where the latter is found. A long series of blood cultures taken by workers in our laboratories from the arm vein immediately or shortly after death, as well as numerous cases reported in the literature, serve to demonstrate this fact. Numerous investigators have further shown that this invasion by streptococci is more commonly antemortem and often occurs as the so-called agonal infection.

[7] Palmer and Henderson, loc. cit.

[1] Read before the American Association of Pathologists and Bacteriologists, Washington, May 10, 1916.

From these cases illustrating the invasive power of the streptococci under definite recognizable conditions of damaged resistance we are able to follow a graded series of cases in which invasion took place hours, weeks, months, and years before death as also innumerable examples when death did not result from the invasion. Many investigators believe that streptococci are frequently invading the body, but that under conditions of relatively good health they are being continually destroyed.

It is certainly true that streptococci invade the blood stream more often than most other bacteria. Their demonstration is not always easy, as they frequently only temporarily invade the blood. It is not uncommon to find that 10 c.c. of blood fails to reveal the organisms while 15 c.c., 20 c.c., or 25 c.c. may be required to demonstrate a single colony. We are limited, for obvious reasons, in the amount of blood we can take, and therefore we endeavor to choose a time when the number of bacteria in the blood is greatest. There is no royal road to successful blood cultures in many of these cases. Serum broth with or without carbohydrates is probably the best medium and by adding a tube of melted agar, anaërobic cultures are readily made. In this as in many similar tests a positive result is important; a negative leaves the question open. There is ample evidence to show that streptococci found in various lesions of the body have probably been distributed by the blood stream, but the invasion from the nearest naturally infected parts of the body must always be first considered.

The portals of entry for streptococci are wide-spread and do not play as important a role in the invasion as is the case with other bacterial groups. The organisms may enter the body from the mucous membranes of the throat, that of the intestinal tract, the uterus, from the skin, and many other points. Naturally, the conditions will vary somewhat according to the types of tissue encountered by the organisms. Whether they further increase in numbers and bring about damage depends largely upon the relative susceptibility or resistance of the different tissues of the body; that is, the environmental conditions they encounter. I do not assume there is a specificity on the part of the streptococci as to what tissue or organ they attack, but, granted that the natural distribution plays no part, I am convinced that they locate in whatever areas offer the proper conditions of relative susceptibility. No two animals offer the same conditions for the invasion of bacteria nor identical susceptibility or resistance in all their tissues. It is true, no doubt, that a group of animals or human beings living under the same conditions will tend, more or less, to similar tissue susceptibilities, and that at different seasons of the year alterations in temperature and moisture of the air, changes in food and ventilation, and number of other environmental conditions will tend to alter these susceptibilities in the entire group.

Nevertheless, certain individual differences will still persist. Many experiments on animals demonstrate this variability in tissue susceptibility in different groups of the same race of animals. Everyone is familiar with family susceptibility as well as individual variations following the same infection. These facts are often forgotten when animals are used in the study of bacteria, but being remembered will often prevent misinterpretation of results.

By virulence of the streptococci I mean something further than invasive power. Virulence is the ability of bacteria to multiply in the tissues, to resist the defensive mechanism, to increase the susceptibility (probably by toxins) of the tissues, and to prepare the way for the manifestations of pathogenicity. If the virulence is high the incubation period is reduced and the pathogenic characters are seen early. It is relatively common in infections with hemolytic streptococci to have a slight local reaction at the portal of entry. The virulence in these cases is very intense and the resistance is rapidly overcome.

Three groups of streptococci have been arranged as follows: (1) Those lacking in invasive, virulent, and pathogenic qualities; these include the strictly saprophytic forms, which I believe are very rare. (2) Those with well-developed, slowly acting virulence (possibly on account of a similarity of metabolic activity to that of the host) but with definite and eventually, when the infection continues, severe pathogenic powers; in this group we have the Streptococcus viridans organisms. (3) Those with powerful invasive power, active virulence setting up violent defensive reactions and exhibiting a high pathogenicity. Under these we have the hemolytic streptococci.

There are a number of conditions that modify the demonstration of these qualities. The portal of entry may be more or less favorable to a rapid manifestation of all these characters. Locally, highly resistant tissues may check either the invasion, the further growth of the bacteria (virulence), or the pathogenicity, while other tissues offer more favorable conditions, particularly mucous membranes in which disease processes, set up by the invading organisms or other bacteria, may offer a ready entrance for the bacteria to underlying structures or the general circulation. The number of bacteria invading the body will also greatly influence the virulence and the pathogenicity. This is particularly to be remembered in consideration of invasion from primary infected foci such as are found in the tonsils, gums, intestinal tract, uterus, and other parts. These local foci also serve as points in which the bacteria may fully develop their invasive, virulent, and pathogenic characters. They serve, as it were, as training grounds for the bacteria. The increase in these qualities is within fairly narrow limits. The hemolytic streptococci, which are the strains capable of becoming highly virulent and pathogenic, may here not only increase in

numbers but develop more rapidly these qualities. The members of the Streptococcus viridans group may also have the opportunity in these foci of increasing in their characters, but only within the limits of the group, and at no time do they develop the type of virulence and pathogenicity found in the streptococcus hemolyticus group.

There is another condition found in these foci which has led to much confusion among early investigators, and that is the presence in them of a mixture of bacteria. Such foci develop as the result of a lowering of resistance in the local tissues and the invasion of bacteria of the grade of virulence proportionate to the condition. Following this several things may happen: the bacteria may increase in disease-producing power within their capabilities or they may prepare the way for more vigorous types of organisms, the two or more growing commensally or until the weaker succumbs. At any time during this process a further invasion of tissue or the blood stream may occur by the original organisms, the mixture, the dominant organisms in the mixture, or by the surviving strains. In any case the organisms invading the body will either be overcome or will cause secondary foci in those tissues in which the environment resulting from the noxious influence of manifold agencies including toxins is favorable for their development.

These possibilities which I have cited are what actually occur. We find infected foci with one type of streptococcus or with two or several types as well as with other bacteria. We can frequently demonstrate the entrance of a new type and its survival in various stages of the process. When the blood stream is invaded it is most commonly by one organism, but by no means infrequently by two. This blood stream invasion is mostly transitory, but sufficient to give rise to secondary foci from which corresponding types of organisms may be recovered. Furthermore, these secondary foci may serve as new distributing points. Wrong interpretations of these findings have led to most astonishing "biological alterations and mutations."

What appears to be the obvious focus of infection is not always the source from which invasion actually occurs. An inflammatory process of the intestinal tract synchronous with pyorrhea, for example, may be the condition leading to the invasion of bacteria. It is, indeed, often extremely difficult to be certain of the conditions present, and we should be very careful in drawing dogmatic conclusions from our necessarily limited findings.

There are certain states of lowered resistance that appear to be favorable for the invasion and activity of one or other of the two main streptococcus groups. In the puerperal state and in scarlet fever the conditions usually favor an infection by the hemolytic streptococci while chronic irritations, such as are found in the stomach, kidneys, and other organs from a variety of causes,

general lack of tone following sedentary life, exposure to cold and dampness, and many other similar, often temporary, lowerings of resistance offer conditions most suited to the attack of the non-hemolytic streptococci. In perforations of the intestinal tract in which the non-hemolytic strains are numerically greatly in excess of the hemolytic, judging from cultures of the intestinal contents, it is usually the latter which survive and cause the severe results, which means that the hemolytic forms can withstand the active defenses of the body better than the non-hemolytic; in other words, they are more virulent.

The members of the hemolytic streptococcus group include the strains with the highest virulence and pathogenicity. They are the causative agents in the most severe types of streptococcal disease, such as severe septicemia, erysipelas, peritonitis, and other pyogenic infections. These infections give severe local or general reactions and are often fatal, but even with recovery we have the clinical picture of severe acute disease.

The streptococci of the viridans group, on the other hand, are the common cause of chronic infections. They have high invasive power and attack tissues in a state of lowered resistance, stimulate little reaction on the part of the body, apparently render the tissues more susceptible to reinfections, and death, if it occurs, only follows after a prolonged course or repeated reinfections. Clinically these cases are characterized by a relatively mild and chronic course with frequent exacerbations. Occasionally a Streptococcus viridans strain prepares the way for a hemolytic strain and the disease becomes a more severe one, and in cases recovering from a hemolytic streptococcus infection an invasion may occur with one of the non-hemolytic forms.

A proper classification is necessary to enable us to recognize the various varieties of streptococci. The method which I have been following for some time and which is published this year has enabled me to greatly enlarge my views on the invasive and other qualities of the streptococci. I have been able to recognize mixtures of different streptococci belonging to both of the two main groups and to trace the source of the invasion in many cases. There is one important point which has been noted in this study, and that is that the streptococci are not specific in their disease production. There is no evidence to support the view that only one type of streptococcus produces endocarditis or nephritis or gives rise to septicemia in the puerperium, scarlet fever, or other conditions of lower resistance. Neither do I believe that one streptococcus is responsible for all the ill effects in all of these cases. Streptococci of several kinds live in symbiosis in the mouth and the intestinal tract. They are often found in mixtures in other infected areas as in the peritoneal, pleural, and other cavities. The blood stream may be invaded by more than one type, although, as a rule, we only

recover one. It is, therefore, not surprising to find different organisms locating in various damaged areas. Under these conditions by the use of the hemolytic test alone we are liable to draw erroneous conclusions. Thus by this single method, without the carbohydrate fermentation tests, the various members of the viridans or hemolytic groups cannot be distinguished.

There are many interesting points for discussion in tracing the source of many of the streptococci. The streptococcic flora of the mouth has always been confusing. The finding of mouth streptococci in the air of rooms as shown by Gordon may be taken as indicating pollution of the air from the oral cavity and thus the flora of the mouth is continually being replenished from the mouths of others. Another source of origin for these streptococci appears to be cows' milk which in turn is subject to contamination from the cows' feces while still a third source is the air streptococcus derived from horse manure. In the mouth cavity many of these strains find favorable conditions for further development. Broadhurst has shown that many streptococci, being swallowed in the sputum, can pass through the stomach without being destroyed in the limited time by the gastric juices. In the intestinal tract the cultural conditions are markedly different from those of the mouth, and many of these strains are destroyed, while others, especially the more vigorous forms, such as Streptococcus fecalis and Streptococcus equinus, flourish and produce a flora quite different from that found in the mouth.

It cannot be too often repeated, however, that the entire flora of any region of the body may be suddenly changed by alterations in the food supplied to the bacteria, the reactions of the secretions, the presence of inflammation, and many other important environmental changes. Particular streptococci finding these new conditions favorable, multiply rapidly and the former inhabitants are crowded out. In diphtheria, for example, streptococci may greatly increase in numbers and seriously complicate the conditions, as has been repeatedly pointed out by Le Gros and others. Although the streptococci present in the greatest numbers in normal saliva and intestines are of the viridans group, a careful search will almost always reveal members of the hemolytic group, and these, as experience teaches, are the strains most capable of producing severe infections. In this connection the influx of strains from disease sources outside of the body, in which the streptococci have developed to a high degree, their disease-producing characters must not be forgotten.

It is beside the point to argue that streptococcus infection in rheumatism and other diseases is a secondary invasion. It is most certainly true that in practically all our infections the bacterial attack is secondary to the necessary conditions of lowered resistance. In many of these arguments one is reminded of Pettenkofer's

demonstration to prove that the cholera vibrio does not always cause epidemics of cholera.

The condition of lowered resistance in the Streptococcus viridans infections are receiving much attention but we are only on the threshold of this study. When the streptococci have established themselves within the system we are usually at a relatively late stage of the disease. Libman has shown that in viridans endocarditis the cases may become spontaneously bacteria-free. The work of many of the German workers would indicate, though on somewhat dubious grounds, that the viridans endocarditis is almost always eventually fatal. There is no doubt that with more careful blood cultures the frequency of viridans infection in the earliest stages is being shown and the recurrent attacks are being guarded against (Oille, Graham, and Detweiler).

Spontaneous streptococcus infections in animals is a frequent occurrence. I have isolated streptococci from about half of 200 guinea-pigs infected spontaneously. In most of these the streptococcus infection was the cause of death, but in others the streptococci were definitely secondary invaders during the course of other infections. In certain animals dying of a hemolytic streptococcus infection of the lungs, for example, non-hemolytic streptococci have been isolated from the peritoneal fluid. I have further demonstrated that streptococci found in the alimentary tract will invade the animal body following injections of dead or living colon bacilli as also after injecting various forms of streptococci. Numerous similar results have been recorded in the literature, but not uncommonly these have been misinterpreted.

It must not be forgotten that in injecting streptococci into animals we are overlooking some of the most important characters of these bacteria. Subcutaneous and intraperitoneal injections of large doses may serve as tests for the further invasive power of the bacteria from these sites, modified by the local injury resulting from the injections, while intravenous injection completely ignores the invasive character. The streptococci by this latter method, finding themselves in the circulation, naturally locate in various organs, and, according to the grade of virulence, will multiply in those tissues in which the susceptibility is of the corresponding grade. The irritation, both mechanical and that arising from the products of growth in the vehicle, will frequently bring about local reactions, which may or may not favor the development of virulence. Infiltration of the tissues with polymorphonuclear leukocytes will frequently follow large injections while only mononuclear response may result from small doses.

Streptococci derived from sources in which the natural infection did not result in a polymorphonuclear reaction may give rise, when injected in large doses, to such a reaction. It is therefore not to be concluded from the unnatural conditions of such experi-

ments that the response elicited is fundamentally characteristic of the bacteria. The study of natural infection demonstrates that the two main groups of streptococci call forth quite different responses, and animal experiments would be of value if we could determine the minimal dose which calls forth any reaction, as this would more nearly approach the natural condition. The products of growth of the bacteria, be they toxins or other excretions, probably determine the character of the response in susceptible tissues, and these two groups differ in the type of reaction they stimulate, the hemolytic streptococci calling forth more active responses and the non-hemolytic a slower and more chronic type of reaction. If we use the same dose of one streptococcus with a certain virulence and find the same tissues affected in the majority of the injected animals it will serve as a test to indicate the susceptibility of these tissues in the particular group of animals. Even varying doses may at times demonstrate the same thing. Further, this same streptococcus having had its virulence raised will attack other tissues which were resistant in the previous experiments. All these and many other points serve to emphasize the importance of the relations existing between the host and the infecting organism.

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REVIEWS

SYPHILIS. By LOYD THOMPSON, M.D., Physician to the Spyhilis Clinic, Government Free Bath House, Hot Springs, Arkansas. Octavo, 415 pages with 77 engravings and 7 colored plates. Philadelphia and New York: Lea & Febiger, 1916.

OBVIOUSLY in the preparation of this work, it has been the intention of the author to present the subject of syphilis as concisely as practicable. Historical and theoretical matters have been given only the consideration commensurate with the practical nature of the book, which although small, is unusually well condensed and one of the best that has thus far appeared. The contents are well divided into three parts: The first comprises a consideration of syphilis in general, with reference particularly to the acquired form; the second is devoted to the various systemic tracts, glands, skeleton, musculature and special organs; the third treats of congenital and regional syphilis.

The author fully appreciates the epoch-making strides that have marked the progress of our knowledge of this disease during the past decade, and accordingly devotes a considerable portion of the work to diagnosis and treatment. The chapter on laboratory diagnosis is especially commendable, although we would censure the author's reliance upon cholesterinized antigen in the performance of the Wassermann reaction.

Thompson appreciates the fact that syphilis is fundamentally a genito-urinary disease, but wisely states that it is a disease requiring knowledge in all fields of medical practice. The author acknowledges his indebtedness to the extensive literature on syphilis, although he has added his own personal views and experiences, as attested by numerous new illustrations in the test. B. A. T.

AMERICAN PUBLIC HEALTH PROTECTION. By HENRY BIXBY HEMENWAY, A.M., M.D. Pp. 283. Indianapolis: The Bobbs-Merrill Company, 1916.

THIS book, in "novel" form, is dedicated to the women of America and is a popular appeal to them, as "the power behind the throne," to use their influence for the advancement of public health. They

are warned that they themselves as amateur sanitarians should not attempt to determine administrative policies or legislative provisions, but are told that their duty above all else lies in encouraging the appointment of competent full-time health officers. It is especially emphasized that practising physicians, both because of their inadequate public-health training and also because of the enmity which is likely to arise between a good health officer and practitioners, should not be health administrators.

Among the other subjects dealt with are the development of public health in the United States, the national health agencies, the changed social and economic conditions due to the advancement in the science of public health, the medical inspection of schools, and the organization of health departments. All these matters are discussed in a popular vein, and yet a great deal is said that is as unrecognized by physicians as it is by the laity. Such books will certainly aid materially in the bringing about of a larger vision of the problem of public health. T. G. M.

THE CATARRHAL AND SUPPURATIVE DISEASES OF THE ACCESSORY SINUSES OF THE NOSE. By ROSS HALL SKILLERN, M.D., Professor of Laryngology, Medico-Chirurgical College; Laryngologist to Rush Hospital, Philadelphia. Second edition. Pp. 418; 287 illustrations. Philadelphia and London: J. B. Lippincott Company, 1916.

MANY changes have been made to the text of the first edition of this excellent work, though, as a rule, these changes consist of adding details and methods heretofore not gone into so elaborately.

Among the newer subjects are Canfield's operation on the maxillary sinus compared with the preturbinal method; also Halle's new frontal sinus operation, with description and illustrations of this method, together with a complete revision of the chapter on the sphenoid sinus.

It is gratifying to note that the author has modified to a great extent some of his ultraradical ideas by giving considerable attention to the phase of treatment which deals with the judgment of the attending surgeon as to whether or not to choose an operative procedure.

The after-treatment of sinus operations is gone into more thoroughly than formerly, and possibly could be dwelt upon even to a greater extent. The end results of sinus operations could also be brought out to better advantage in spite of the addition of a compilation of the American mortalities following the Killian operation.

The work, as a whole, meets the demand for a clear and concise treatise on nasal sinuses and their operations. The author not only writes from his own personal view-point, but also has, whenever possible, mentioned other methods, with copious references to the literature on the subject.

There is possibly no work in the English language that better meets the aim of this book, namely, that of presenting an exclusive treatment of the nasal sinuses, meeting the demand both of a text-book and one of reference. B. D. C.

SEXUAL IMPOTENCE. By VICTOR G. VECKI, M.D., Consulting Genito-urinary Surgeon to the Mt. Zion Hospital, San Francisco. Fifth edition. Pp. 405. Philadelphia and London: W. B. Saunders Company.

SINCE 1888, when the first edition of this book was published, the development of the science of euology has made possible more accurate diagnosis and consequently a better therapy for sexual impotence. The author has revised and modified the work for this edition chiefly from the stand-point of treatment, but his ethical and sociological views remain unchanged, though they differ in many respects from those generally held by the profession. The well-written chapters on anatomy and physiology are followed by an elaborate description of the forms of impotence. The chapters on diagnosis and prognosis are disappointingly brief.

In the chapter on treatment the author discusses all the usual and nearly all the unusual drugs and therapeutic methods. He says: "The great number of methods and remedies speaks for the small value of most of them, and yet there is hardly any one of them that could be entirely dispensed with." The excellent table of contents and index are useful in correlating the text, which has a tendency to be vague in its application. The printing and binding are up to the usual excellent standard of the publishers.

G. M. L.

WHAT TO EAT AND WHY. By G. CARROLL SMITH, M.D., Boston, Mass. Second edition, thoroughly revised. Pp. 377. Philadelphia and London: W. B. Saunders Company.

THIS book is primarily intended for physicians, but is written in a semipopular style. Under the caption of various diseases it considers foods and diets which, in the opinion of the author, are suitable to these respective conditions. There is contained a good

deal of useful information together with rather individual generalizations which are of less value. Certain important phases of treatment are omitted, as, for example the "starvation" treatment of diabetes, and there are included such sections as that on "diet in uric-acid diathesis." The language is rather loose in structure, and in some places ungrammatical. R. P.

DER STARRKRAMPF, SEINE ENTSTEHUNG UND BEHANDLUNG. von Prof. Dr. FERDINAND BLUMENTHAL, Leitender-Aerzt der inneren Abteilung des städt. Krankenhauses Berlin-Lichtenberg. S. 79. Wien: Verlag von Urban & Schwarzenberg.

THIS brochure is extracted from Blumenthal's article upon tetanus, which appeared the previous year in Eulenburg's *Real-Enzyklopädie*. It was published separately by the author at the request of numerous physicians who found themselves suddenly confronted with tetanus in the European War when, as a matter of fact, they had seldom or never seen a case of the malady previously.

The brochure opens with a description of the incidence and natural history of tetanus, and then discusses human tetanus, experimental tetanus, disposition and natural immunity, methods of conferring immunity, metabolic changes, serum treatment, prophylactic treatment with antitoxin, serum preparations, serum anaphylaxis, other methods of treatment, symptomatic treatment of the convulsions, and the feeding of tetanus patients.

The brochure is written by an authority on tetanus, and its perusal shows that the disease is a very interesting one to study. The author presents the most modern and accepted form of treatment, which is quite the same as that used in our own great metropolitan hospitals. The monograph is timely and useful.

P. G. S., JR.

CEREBELLAR ABSCESS: ITS ETIOLOGY, PATHOLOGY, DIAGNOSIS, AND TREATMENT, INCLUDING ANATOMY AND PHYSIOLOGY OF THE CEREBELLUM. By Drs. ISIDORE FRIESNER and ALFRED BRAUN. Pp. 186. New York: Paul B. Hoeber Company, 1916.

THE authors begin with the anatomy of the cerebellum, in which many diagrams are used to illustrate the connections of the cerebellum with the cerebrospinal system.

The next chapter concerns itself with the physiology of the cerebellum, in which the various opinions of those who have worked in this field are presented, there being a short summary of Barany's

investigations and his tests. Then follows the etiology and pathology of cerebellar abscesses. This undoubtedly is the best part of the book, and gives the experience of the authors in this field. In the next chapter advantage is taken of the recent literature, and the symptomatology of the cerebellum is presented perhaps better than is the case with most text-books. In common with most articles on cerebellar symptomatology, however, they still cling to the idea that a cerebellar lesion should give a certain group of symptoms, such as hypermetry, asynergia, tremor, disturbances of tone, etc., when, as a matter of fact, they all depend upon the one primary disturbance of function due to a lesion of the cerebellum, that is, asynergy. This, however, is a minor error, for the important thing is that all the symptoms are given, and anyone reading this chapter would undoubtedly attain an adequate idea of cerebellar symptomatology. The illustrations of the pointing tests are not adequate. The last chapter concerns itself with prognosis and treatment. The authors rightfully assume that early surgical measures should be employed. They give an adequate review of the literature and their own experiences.

On the whole, this book represents a very good attempt to present the subject of cerebellar abscess, and is adequate when it is considered that it will be read mostly by others than neurologists. It is always rather risky for a specialist to write upon a subject which is not particularly in his field. If, for example, a neurologist should essay to write about a nose, throat, and ear condition he would naturally fall into many errors, for he could hardly be expected to know the subject as well as those who limit their work to these subjects. The reviewer, however, has no doubt that in subsequent deserved editions of this work such errors will be eliminated. T. H. W.

SYPHILIS AND THE NERVOUS SYSTEM. By Dr. MAX NONNE. Authorized translation from the second revised and enlarged German edition. By CHARLES R. BALL, M.D. Pp. 450; 98 illustrations. Philadelphia and London: J. B. Lippincott Company, 1916.

THE second edition of Nonne's book is a vast improvement over the first, the review of which was published in this JOURNAL some years ago. Practically no changes have been made in the presentation of the organic matter, for the symptoms of involvement of the nervous system are the same now as they always have been.

When the first edition was written the Spirochete pallida, the application of the Wassermann and other serum tests, to which the author has contributed largely, and the use of salvarsan were just becoming known. Therefore, there is scarcely any mention

of these matters in the first edition. In this work the serum tests, especially Nonne's own tests, are elucidated and their value shown. It is hardly necessary to comment on this subject, for it is well known to the profession and Nonne does not present anything that is new. His views, however, upon the use of salvarsan in syphilis of the nervous system are very important. He is of the opinion that salvarsan in individual cases gives a quicker and a more far-reaching result than may be obtained with the use of mercury and iodide, but he says that in by far the greater number of cases the superiority of salvarsan over mercury and iodide is not apparent. In cases of gummatous disease of the central nervous system immediate salvarsan treatment may be said to be especially indicated. In specific disease, in which the vital centers are involved, it is especially contra-indicated. He does not think it is of more value than mercury in tabes nor of more value than mercury or iodide in paresis. He does not see any special advantage in the Swift-Ellis serum treatment. He advises the combined use of salvarsan and mercury. He quotes a number of instances in which cases of undoubted paresis have been cured. Some of these he had under his observation for over twenty years. To anyone interested in syphilis of the nervous system this excellent translation of Nonne's book gives by far the most adequate presentation of the subject.

T. H. W.

ANNUAL REPORT OF THE DEPARTMENT OF PATHOLOGY OF THE JOHNS HOPKINS UNIVERSITY AND HOSPITAL I. The Johns Hopkins Reports, Vol. XVIII, Fasciculus I. Pp. 102. Photographs, drawings, charts, and tables. Baltimore: Johns Hopkins Press, 1916.

THE volume is the first issue of the annual report of the department of pathology and embraces abstracts of the articles which have already appeared and short outlines of work which had not yet been published in scientific periodicals at the time the volume was printed. A brief review of the original articles given in full and those abstracts in which there is no promise of further report is here given.

Goodpasture and Clark describe the isolation of a toxic, thermostabile element associated with beta-nucleoproteid in pancreatic tissue. This substance is probably proteid, as it gradually autolyzes to destruction, is not due to the action of trypsin, and is toxic for animals.

Schmeisser and Winternitz present data going to show that the acute and subacute diseases of the fowl, fowl typhoid, and leukemia are due to Moore's Bacteria sanguinarium, and are in all probability phases of the same infection.

Winternitz's work supports the theory that the islands of Langerhans may be qualitatively or quantitatively altered in diabetes, that their significance is not understood, and that the pancreas is but "one link in the chain that controls carbohydrate metabolism."

The same author reports a case of generalized miliary tuberculosis resulting from an extension of a tubercular pericarditis into the right auricle. (Without desiring to be captious the reviewer thinks it is better to use the adjective "tuberculous" for a lesion due to the bacillus of Koch.)

An interesting case of acute hyphophysitis arising by extension, reported by Boggs and Winternitz, showed no hyperglycemia, glycosuria, or localizing signs.

More interesting case histories close the scientific reports in the volume.

The last few pages are devoted to a description of the workings of the department of pathology. The 5000 autopsy records collected in seventeen years are to be combined in a single volume, ready in 1917, according to a plan worked out by a statistician of a large insurance company coöperating with the pathologists. Sample charts and filing cards are depicted. The classifications are only in gross organ systems, and the diagnosis will have to be inserted in symbols. It is not quite clear how the record book and filing cards are to be completed. The latter seem too comprehensive for a mere index and too small for a protocol. Autopsy records for the past five years arranged according to service and percentage show a distinct increase in number. The pathological and clinical staffs have conferences each week upon autopsies performed. Further coöperation is indicated by an attempt to have junior members of the clinical staff working in the laboratory.

The book is a distinct stimulus to community of interest between those at the bedside and those at the autopsy table. The reports are especially commendable in their brevity. H. F.

AMERICAN YEAR-BOOK OF ANESTHESIA AND ANALGESIA. By F. H. McMECHIN, A.M., M.D. (Editor). Pp. 415; illustrated. New York: Surgery Publishing Company, 1916.

THE editor states that this year-book was established for the collation of the world's ultrascientific researches for the practice of anesthesia and analgesia and that the contributors have scoured the world's literature to make the context as comprehensive and exhaustive as possible. Thirty-one papers are presented by representative writers, and while original research has been given a prominent place the clinical aspects have by no means been neglected. Besides a general survey of the progress being made in these subjects,

there are provided those special advances having a direct bearing on the individual requirements of the practising surgeon, dentist, anesthetist, etc. The thirty-one papers cover pretty much the whole field of anesthesia and analgesia. The following are a few of the clinical subjects discussed: Chloroform poisoning; use of music in anesthesia; effect on kidney function of anesthesia; manufacture of nitrous oxide for hospitals; ether-colonic anesthesia; nitrous oxide in obstetrics; somnoform in dental operations; local anesthesia in connection with after-pain for ano-rectal surgery, for hernia operations, and for prostatectomy. There is one paper on injecting the Gasserian ganglion and two on spinal anesthesia. When one wishes to use any of these forms of anesthesia this work must be of great service in furnishing full information in each instance. T. T. T.

THE PRACTICE OF OBSTETRICS. By J. CLIFTON EDGAR, Professor of Obstetrics and Clinical Midwifery in the Cornell University Medical College; Visiting Obstetrician to Bellevue Hospital, New York City; Surgeon to the Manhattan Maternity and Dispensary; Consulting Obstetrician to the New York Maternity and Jewish Maternity Hospitals. Fifth edition, revised. Pp. 1024; 1316 illustrations. Philadelphia: P. Blakiston's Son & Co., 1916.

THE present volume follows closely the lines of the previous editions, and for this reason an extended comment seems unnecessary. The revision, if it can be so termed, consists in the addition of a few pages on painless labor and twilight sleep, pituitary extract in uterine inertia, and the artificial feeding of infants.

The introduction of pituitary extract must rank as one of the important recent advances in obstetrics. However, the usefulness of the drug is counterbalanced with possible dangers to the mother and child from its use. The author reviews the indications for its administration, cautioning against the uncertainty of its action in some cases. Among the contra-indications omitted is that of using this drug in cases with high arterial tension, as in toxemia of pregnancy. Anyone who has had a considerable experience with pituitary extract in labor will agree with the author that "it should not be employed for inertia in any stage of labor unless anesthesia is at hand for immediate use, and preparation complete for immediate operative delivery, if necessary."

From a study of a sufficiently large number of parturients treated with morphin and scopolamin in an effort to secure the so-called twilight sleep, the author concludes that the method is not entirely free from danger to the two parties concerned. He has found labor prolonged, operative interference more frequently demanded, with a

higher percentage of maternal traumatism, and an increased degree of cyanosis and asphyxia in the infant, with an occasional stillbirth from the use of morphin and scopolamin. He draws more favorable conclusions regarding the use of nitrous oxide and oxygen analgesia in labor.

The chapter on artificial feeding of infants has been considerably changed and new tables of formulas added. A new type of lung-motor for the treatment of asphyxia and a new type of incubator for premature children are pictured.

The book will undoubtedly continue to be regarded as a standard authority on obstetrics. P. F. W.

THE DREAM PROBLEM. By DR. A. E. MAEDER, of Zürich. Nervous and Mental Disease Monograph Series, No. 22. Pp. 43. New York: Nervous and Mental Disease Publishing Company, 1916.

THIS is No. 22 of the monograph series issued by the *Journal of Nervous and Mental Disease*. This small essay of 43 pages is a paper read at the Congress of the Psycho-analytical Society at Munich, September, 1913, published in the *Jahrbuch f. Psychoanalyse und psychoanalytische Forschungen*, 1914. The paper concerns itself with the certain phases of the dream problem. A difference of opinion has arisen as to the interpretation of dreams between Freud and the so-called Zürich school led by Jung. The author, while giving credit to Freud that neurotic symptoms must be regarded as unsuccessful attempts at cure, seeks to establish that the axiom of the dream as a wish-fulfilment is too indefinite, for it fails to embrace the important teleological side of the unconscious function. Maeder regards the dream as the means of expression of the unconscious, and tries to show there is a constructive phase, and that one should regard the dream not only as a problem of wish-fulfilment but also as an effort at cure. He gives an interesting analysis of a patient and compares his interpretation with that of Freud. To psychoanalysts this paper is, of course, very interesting. To those not believing in psychoanalysis the paper is, nevertheless, interesting reading. T. H. W.

INSTINCT AND INTELLIGENCE. N. C. MACNAMARA. Pp. 216. London: Henry Frowde, Oxford University Press. Hodder & Stoughton, Warwick Square, E. C.

PERHAPS the best idea of this book is expressed in the author's preface: "The meaning of the term education is 'to draw out what is in a child;' it therefore includes the training of his inherited instinc-

tive disposition or character as well as the 'putting in' needful knowledge or the 'instruction' of his intellectual faculties. Educationists of the present time appear to exaggerate the importance of training the intellect, and are apt to overlook the fact that each individual possesses certain instinctive qualities which to a large extent determine his behavior throughout life. These qualities, which no human power can eradicate, may, however, be favorably modified by appropriate training. In the following pages we have endeavored to give an outline of the evidence, and the reasons upon which we rely to prove that the instinctive behavior of human beings depends on work performed by definite parts of the brain; consequently, education has not only to deal with the training of something immaterial which we call mind or consciousness, but has first and foremost to deal with the proper development of the nervous substance of that part of the brain the orderly working of which is essential for the occurrence of instinctive, and intellectual phenomena."

The author then begins with the anatomy and physiology of the ameba and then goes on from this to the higher animal until he finally arrives at the nervous structure of the human being. He advocates the free play of children's actions and is an advocate of the Montesson system.

The book necessarily is very sketchy, but gives an adequate idea to those who wish to have a clearer knowledge of the nervous anatomy, which is the basis of all instinct and intelligence.

T. H. W.

HAND-BOOK OF MASSAGE FOR BEGINNERS. By L. L. DESPARD, Member and Examiner, Incorporated Society of Trained Masseuses. Pp. 247; 88 illustrations. London: Henry Frowde and Hodder & Stoughton.

THIS is an admirable book in which the subject is very simply treated. Mention is made in the introduction of carrying on the work under the direction of a physician, and appropriate stress is laid upon the limitations of this form of treatment.

Chapter I treats of the manner in which massage and exercise affect the body's tissues and fluids.

Chapters II, III and IV describe the various movements (active and passive) necessary in applying general and special treatment.

Chapters V to XII deal with the treatment of diseases and deformities in which manual methods have been proven useful.

A useful chapter on Bandaging and a short one on War Injuries are followed by the last chapter, which treats of Medical Electricity.

E. C. L.

THE BOOK OF THE FLY. By G. HURLSTONE HARDY. Pp. 124; 6 figures and 7 plates. New York: Rebman Company, 1916.

AT this time when the method of disease dissemination is a matter of such vital importance this book on the fly question becomes of especial interest and value. The major portion of the volume is devoted to the general life history, anatomy and diverse habits of the various varieties of flies. This of necessity makes much of the book somewhat tedious for the lay reader, with its scientific terms, and to the naturalist it presents nothing new. The chapters dealing with methods for the extermination and control of the fly nuisance are attractive and of considerable value. The whole book is well written and remains a complete presentation of the fly problem. As such it must take its place in the history of the battle being waged for the extermination of this pest. T. G. S.

A REPORT ON RESEARCHES ON SPRUE IN CEYLON. By P. H. BAHR, M.A., M.D., D.T.M. and H., M.R.C.P., M.R.C.S. Pp. 155; 9 illustrations. London: Cambridge University Press.

WHILE not on a subject of every-day interest to the physician of the temperate zone, this monograph makes interesting reading. It is clear that the author has investigated his subject with great zeal and care, and has applied all the resources of modern medicine to his task. Some of the researches seem to point to the conclusion that an infection with the thrush fungus is the cause of the disease. The book is well arranged, and the illustrations are unusually well produced. A. G. M.

NERVOUS CHILDREN. By BEVERLEY R. TUCKER, M.D. Pp. 510. Boston: The Gorham Press, 1916.

THIS book is just what it claims to be, a bugle call to the army of workers with children to "prevent" instead of "cure." It opens with a very general description of the physiological basis for nervousness and leads on through successive chapters on heredity and environment, sexual hygiene, and the training of nervous children, up to an outline of nervous and mental diseases of childhood. The book gives little definite advice except perhaps in the chapter on "habits." It makes excellent and profitable reading for those who wish to know this subject from the stand-point of discovering (but not especially helping) that ever-present product of our civilization, the nervous child. A. G. M.

THE ALLIGATOR AND ITS ALLIES. By ALBERT M. REESE, Professor of Zoölogy in West Virginia University. Pp. xi, 342; 52 figures; 28 plates. New York: G. P. Putnam's Sons.

ALTHOUGH regarded by the publishers as a book of general appeal, this treatise will doubtless find a large acceptance only in the hands of specialists in herpetology and embryology. The only part which might concern others is the first chapter on the biology of the crocodile. While in part a compilation of information regarding this group of reptiles, there is much of original information coming from the author's somewhat extensive experience with the American forms. This is particularly true of the chapter on the development of the alligator, which occupies one-third of the book, and is a reprint, in part, of an earlier paper. The illustrations, many of them original, are good and the typography is excellent.

McC.

CEREBROSPINAL FEVER. By THOMAS J. HORDER, M.D., Assistant Physician to St. Bartholomew's Hospital. Pp. 179; illustrations 17. London: Oxford University Press.

THIS small book is essentially a monograph on the subject of cerebrospinal fever. It is called forth by the present prevalence of the disease in England, and among English troops. There is interesting history which notes the various epidemics occurring since 1805, when cerebrospinal fever was first recognized as an entity. Especial mention should be made of the chapters on modes of infection and prophylaxis. Indeed, the treatise is quite complete, and all that is definitely known of cerebrospinal fever is to be found clearly stated in an easily accessible form.

A. G. M.

MEDICAL HINTS. By COLONEL J. EDWARD SQUIRE, M.D., F.R.C.P., D.P.H. 128 pages. London: Oxford University Press.

IN reading this book one cannot but be impressed with its value for those for whom it was written—namely, the medical officers of an army. It is refreshing at a time when so much surgical is to be read of war to find this little volume devoted to things medical. The more common medical conditions to be met with in war time are concisely dealt with. There are excellent chapters on parasites and poisons, including bichloride, alcohol, and tobacco, and the remarks about malingering and marching are especially noteworthy.

A. G. M.

THE ADOLESCENT. By J. W. SLAUGHTER. Pp. 100. New York: The Macmillan Company.

ANYONE who is searching for a study of the psychology of the adolescent will read this book with much pleasure and profit. The explanation of mental processes, desires, actions and motives is usually clear, and reflects a vast knowledge of youth. The unfolding of the mind and emotions in an individual is compared to the evolution of the race as a whole. By clear reasoning it seems proved that civilization and a prolongation of adolescence are found together.

Valuable chapters point out the difference between the education of boys and of girls. Juvenile crime, skepticism, adolescent love, and the normal development of the instincts and emotions are other subjects dwelt on in an interesting manner.

The book is especially recommended to teachers. One cannot but wish that he had had someone with the understanding of the author to conduct him through the "storm and stress" of his own adolescence. A. G. M.

BACK INJURIES AND THEIR SIGNIFICANCE UNDER THE WORKMEN'S COMPENSATION AND OTHER ACTS. By ARCHIBALD MCKENDRICK, F.R.C.S.E., Surgeon in Charge of Surgical Roentgen-ray Department, Royal Infirmary, Edinburgh. New York: William Wood & Co., 1916.

THIS book consists of 173 pages and 14 illustrations. The medico-legal aspect of back injuries is emphasized in the preface and also in the context. The first 34 pages treat anatomy in detail. A few pages are devoted to stress and contusions of muscles, also to the healing process. A small portion is devoted to surface anatomy. The mode of examination of the patient and the significance of the history and subjective and objective symptoms have received more or less of careful attention.

The heading Examination is interspersed with anatomical, pathological, and physiological facts. The significance of the Roentgen ray is moderately emphasized.

A considerable portion of the book is devoted to dynamics, under which heading external and intrinsic stress, as applied to this part of the anatomy, and its effect upon the structures, is more or less carefully figured out.

The book to a rather considerable extent is elementary, especially in its dealing with anatomical facts. It is somewhat desultory and poorly arranged. In many places it is unconvincing; however, it is a collection of very useful facts, which should be of decided value to the person interested in back injuries. W. J. M.

PRACTICAL PRESCRIBING AND TREATMENT IN THE DISEASES OF INFANTS AND CHILDREN. By D. M. MACDONALD, M.D., F.R.C.P.E. Pp. 193. London: Oxford University Press.

IN this little book the author attempts to point out some diffences between dosage of drugs in children and adults, and to give brief outlines of treatment in certain of the more common diseases and conditions of childhood. In the first chapter is a plea for carefulness in prescribing and avoidance of certain incompatibilities. There is a chapter on infant feeding which is notably brief. The diet tables contain none of the newer preparations, such as casein milk. The chapter on emergencies contain some helpful suggestions, although the section which deals with the treatment of specific diseases is incomplete even for so small a manual.

It would seem that the book is of little value to the specialist, although it might be of some small service to the general practitioner dealing with children. A. G. M.

THE AFTER-TREATMENT OF OPERATIONS. By P. LOCKHART-MUMMERY, F.R.C.S. Eng., B.A., M.B., B.C. Cantab., Senior Surgeon, St. Mark's Hospital for Cancer, Fistula, and other Diseases of the Rectum; The Queen's Hospital for Children, London; Honorary Surgeon to King Edward VIIth's Hospital for Officers; Special Consulting Surgeon to City of London Military Hospital and Fulham Military Hospital; Jacksonian Prizeman and Late Hunterian Professor, Royal College of Surgeons. Fourth edition. Pp. 275; 39 illustrations. London: Ballière, Tindall & Cox. New York: William Wood & Co.

FOR the general after-treatment of operation cases this manual fills an important place, and from the very comprehensive way in which the subject is presented it should be in the hands of every house surgeon and general practitioner.

In the present edition much new matter has been added, especially a chapter on the treatment of gunshot wounds, and the chapter on surgical shock has been entirely rewritten, being chiefly a summary of Crile and Lower's contributions on this subject.

The book is well edited and the illustrations are attractive and helpful. Throughout the text there are numerous foot-note histories of cases very aptly illustrating the condition under discussion. There are also many references to the literature. J. C. B.

PROGRESS
OF
MEDICAL SCIENCE

MEDICINE

UNDER THE CHARGE OF
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Studies on the So-called Transitional Cells.—Evans (*Arch. Int. Med.*, 1916, xviii, 692) in the present study has made the attempt to clear up some of the uncertainty which exists in regard to the large mononuclear white blood cells, concerning the various types of which, their origin and significance a great deal of confusion exists. In this group the so-called transitional cells stand out from all the rest by reason of their content in granules of an oxydase ferment, as can readily be demonstrated, by the application of the indophenol-blue reaction. Taking advantage of this fact the author has attempted by means of experimental methods, to determine *first* which of the mononuclear wandering cells of the tissues, if any, are lymphoid and which histogenous; *second*, which of the large mononuclear cells of the blood fall into the same groups; *third*, whether the transitional cells of the peripheral blood can be identified with any other mononuclear cells of the blood or tissues; and *finally*, whether all the mononuclear wandering cells of the body exclusive of the small lymphocytes, are of histogenous origin. He has attempted to solve these points by a number of methods including intravenous vital staining, and intraperitoneal vital staining, using various types of dyes. As a result of his studies Evans gives the following grouping of the mononuclear cells: (1) Cells containing an oxydase ferment and not taking the vital stains. (2) Cells containing no oxydase ferment but specifically stained intra vitam. These cells are the normal constituents of the tissues and are of rare and accidental occurrence in the peripheral blood. (3) Cells containing no oxydase ferment and not taking the vital stain, namely the lymphoid elements in which are included the true lymphocytes and probably most of the non-oxydase large mononuclears of the blood. These observations

would seem to refute the theory of Mallory which assumes that all the adult mononuclears of the blood are of endothelial or histogenous origin and supports the view of Aschoff that there is a distinct histogenous and lymphoid group of cells totally distinct from each other. With specific reference to the transitional cells Evans points out that they constantly present the following features: (1) They possess an oxydase ferment readily demonstrable. (2) They are not specifically stained intra vitam. (3) They take up carmin particles from an unfiltered solution. (4) These cells may be found in the spleen and other blood-forming organs, but are not more abundant in the splenic vein blood than elsewhere and are never seen in the omentum, serous fluid or tissues when any polymorphonuclear cells are present. (5) And finally, the evidence is in favor of the view in accordance with that supported by Naegeli, that these cells belong to the granulocyte series and, together with the other granular polynuclear cells, should be regarded as descendants of the myeloblasts of the bone marrow and splenic pulp.

Autogenous Defibrinated Blood in the Treatment of Bronchial Asthma.—Kahn and Emsheimer (*Arch. Int. Med.*, 1916, xviii, 445) have devised a rather interesting method for the treatment of bronchial asthma consisting of the subcutaneous injection of autogenous defibrinated blood. This blood is withdrawn whenever possible, during an asthmatic attack. The theory upon which they base this mode of treatment may be stated in the following way: asthma is presumably due to a spasm of the smaller bronchi and this spasm in turn is probably the manifestation of an anaphylactic condition. It is presumed that the anaphylactic phenomenon represented by an attack of bronchial asthma is to be explained upon the basis of protein sensitization, though whether the protein gains access to the body by the nasopharynx, gastro-intestinal, or respiratory system is not certain. In any event, it is probably absorbed into the blood, and if so, it should be found there most probably just prior to or during an acute asthmatic attack. If these assumptions are true, then it is quite conceivable that immunization by the repeated parenteral injections of autogenous defibrinated blood should be beneficial to the patient. Applying this theory, the patients have secured, in six successive cases, of bronchial asthma, very favorable results as shown by definite improvement generally and a decrease in the frequency and severity of the bronchial asthma attacks. The patients have been able to do more work and have gained in eight. The procedure is simply the withdrawal of about 20 to 30 c.c. of blood into a sterile flask which contains a number of glass beads. By agitation the blood is defibrinated and it is then immediately injected subcutaneously into the loin of the patient. Aside from a little local discomfort, there have been no untoward effects following the injections.

The Relation of the Pituitary Body to Renal Function.—A great deal of work has been done recently in an attempt to demonstrate a relationship between the pituitary body and the kidneys, especially with regard to the etiology and pathology of diabetes insipidus. In the present article Motzveldt (*Jour. Exp. Med.*, 1917, xxv, 153) brings forward further evidence to support a conclusion previously advanced by him to the effect that the pituitary body exerts its essential action

upon the kidneys in the way of *checking* the flow of urine or in other words, the function of the pituitary body with relation to the kidney is one of an anti-diuretic effect, this action being most marked when diuresis is high. In support of this contention the author has previously shown the beneficial effects which have persisted over a period of two years in a case of diabetes insipidus treated with the posterior lobe of the pituitary body. In the present work a more or less constant artificial polyuria was worked out in rabbits by introducing into their stomachs between 150 to 200 c.c. of water. Curves of excretion were thereafter charted out for various rabbits treated with pituitary extracts of a number of different preparations. In addition to noting the effect of pituitary extract, the effects of other drugs such as chloral, strychnia, morphin, caffein, adrenalin, thyroid and thymus glands were noted all under different conditions of administration and both with and without the intermediate action of the nerve supply to the kidneys. As a result of the study the author again comes to the conclusion that extracts of the posterior lobe of the hypophysis, whether given by mouth, subcutaneously or intravenously, are able to check an induced polyuria. This anti-diuretic effect is apparently independent of the changes in the blood-pressure, intestinal absorption or the action of the vagus nerves. One very interesting feature and of practical therapeutic importance was the beautiful demonstration of the fact that the anti-diuretic action of the pituitary is absent or only slightly present, in checking the so-called salt diuresis produced, in this instance, by the ingestion of 40 c.c. of a 10 per cent. solution of sodium chloride. This fact is a further demonstration of the essential difference between water diuresis and salt diuresis and shows the importance of a salt-poor diet in the rational treatment of diabetes insipidus.

Renal Function in Pernicious Anemia. — It has been previously pointed out that patients with severe anemias may give results to a renal test diet which are similar in every detail to those found in advanced cases of contracted kidney. The point first emphasized by Mosenthal has been further studied by CHRISTIAN (*Arch. Int. Med.* 1916, xviii, 430) in a series of cases of pernicious anemia. The data secured from this study indicates without doubt that in severe anemia renal function as measured by diet tests, is disturbed in much the same way as in cases of advanced chronic interstitial nephritis. This is apparently true no matter whether the anemia is in a young or old person. It would seem most likely that the disturbance of renal function is a direct result of the anemia and is the expression either of a nutritional or of a toxic disturbance in the activity of the renal cells. Evidences in favor of this view are shown by the improvement in renal function which takes place parallel with an improvement in the anemia itself. In view of the fact therefore that an advanced nephritic picture may be entirely simulated by cases of severe anemia, it is absolutely necessary to consider the element of anemia whenever one attempts to draw conclusions from renal test diets applied to patients with nephritis. Christian points out however, the fact that this point, though of great importance, is not going to prove a very complicating factor, since, despite their pallor, the degree of anemia in patients with advanced nephritis is very often slight.

SURGERY

UNDER THE CHARGE OF

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The Antiseptic Treatment of Wounds.—FELDMAN and WALTON (*Lancet*, December 23, 1916, p. 1043), from a large military experience, deduced the following as the best antiseptic treatment for wounds: The antiseptic, itself, was prepared by rubbing together in a mortar crystals of pure carbolic acid and camphor in equal parts by weight—a perfectly clean sweet smelling liquid being thus obtained. As is the case when using any other application, it is primarily essential to provide adequate drainage. When seen in a relatively early stage the wound, if deep or punctured, should be opened under general anesthesia so as to eliminate, as far as possible, any pockets in the tissues and all foreign bodies, loose pieces of bone, or necrotic tissue should be removed. When the wound has been freely opened sufficient of the liquid is poured in to reach the whole surface of the tissues. In large wounds as much as one or two fluid ounces may be required, although as a general rule one or more fluid drams are sufficient. Drainage tubes are inserted as required and packed around with gauze soaked in the fluid. On the surface dry gauze is applied. It is only necessary to change the dressings every forty-eight hours, when a few drops of the fluid are dropped down the tube and fresh soaked gauze applied to the raw surfaces. When the treatment is commenced some days or weeks after the infliction of the wound it is again necessary to open up all sinuses and pockets so that the fluid may reach all the septic areas, and if necessary tubes should be inserted so that free drainage is established. The fluid is then used in the same manner as previously. It is noteworthy that the fluid can be handled freely without doing any harm to the skin. but if left for a prolonged period in contact with the patient's skin around the wound a certain amount of burning may be caused. For this reason surface dressings should be formed of dry gauze. It is rarely necessary to smear the surrounding skin with sterilized vaseline. The following claims are made for the treatment: It overcomes sepsis more rapidly than other methods. With its use amputations are much less frequent. It diminishes pain rather than increases it as is so often the case with other dressings. The dressing requires to be changed only at long intervals. Its use is associated with no danger. The amount of work in the ward is greatly diminished. It is most suitable to the conditions of modern warfare.

Tissue Fragments and Wound Infection.—TAYLOR (*Ann. Surg.*, 1916, lxiv, 641), in connection with his military hospital work in France, carried out a series of experiments on guinea-pigs to determine the parts played by missiles, fragments of clothing, and detached or severely

traumatized tissue fragments, in carrying loads of bacteria and acting as foci of infection. The result of the experiments suggests that in the cleaning of fresh wounds at least as much care should be exercised to remove separated and devitalized fragments of tissues as is taken to remove other foreign bodies. In all operative procedures where blunt dissection is practiced it should be remembered that torn fragments of devitalized tissue may remain to become a ready soil for the incubation any bacteria which may gain access to the wound.

Blood-pressure and Graphic Vasomotor Changes in the Periphery During Ether Anesthesia.—Muns (*Ann. Surg.*, 1916, lxiv, 645) says that in a former paper he studied the changes occurring in the peripheral vessels during shock brought on by intestinal trauma. The animals used were anesthetized with ether, and the question arose as to what depressing, exciting or neutralizing effect the anesthetic may have had on the vasomotor mechanism. He carried out a series of experiments on dogs to study these effects, with the following results: Ordinary third-stage ether anesthesia prolonged beyond one hour results in more or less marked vasodilation in the periphery. This is a progressive change, more or less regular in character, increasing directly in proportion to the lengthening time of administration. In most cases the limit of vasodilation is not reached seven hours after the beginning of the anesthetic, but occasionally the extreme of the condition may be reached after a shorter administration of ether. There is a direct relationship between the condition of the vasomotor control and the blood-pressure. The end-result of ether depression is loss of function. The symptom-complex, known as post-operative shock, is a combination of the effects of excitation and depression, and varies direction with the algebraic sum of these two factors. The vasomotor center is the variable factor in bringing about the vasomotor change; the variation of response is directly dependent upon the changes in the vasomotor center produced by ether.

Blood-pressure and Prostatectomy.—Peacock (*Ann. Surg.*, 1916, lxiv, 659) says that there is a vital and definite relationship between the vascular system, and the renal functionating which is measured by the blood-pressure. And as old age and obstruction of the lower urinary tract greatly raise this pressure, we view with interest anything which suddenly decreases it, as serious complications often result. On the basis of seven prostatectomies in which blood-pressure observations were made, he found that there is a definite physiologic relation existing between the blood-pressure and the filtration in the kidney glands. That a high blood-pressure is purely compensatory, and necessary to the individual in which it is found, to maintain a normal excretion of urine. That any sudden and permanent lowering of the blood-pressure by radical or heroic measures is often a fatal procedure. That a persistently high blood-pressure, even in the absence of albumin and casts, usually means a hidden nephritis. That a chronic prostatic obstruction produces serious back pressure changes in the ureters, the kidney substance, the kidney circulation and the excretion of urine. That a sudden relief of this intravescial pressure produces an immediate fall in blood-pressure, from 20 to 100 mm. Hg. That if the pre-operative blood-pressure is much over 150 mm. Hg, the risk of a cystotomy or

prostatectomy increases rapidly. That compensation between the blood-pressure and the urinary excretion will take place if the pressure is not abnormal and will occasionally in a high pressure where there is unusual vitality or compensatory power.

Spondylitis Deformans Relieved by Albee Operation.—FINKELSTEIN (*Ann. Surg.*, 1916, lxiv, 713) says that of all the ills that man is heir to, none can claim priority over spondylitis deformans as a deforming and disabling disease, not only because of its chronic progressive nature, but also because of our inability either to check its progress or to relieve its distressing symptoms. The spondylitis in this case began with a severe injury of the spine, twenty-eight years before operation, but it was not until twenty-two years later that working became a hardship. For five years he received non-operative treatment, including the use of a plaster cast. The Albee operation was performed in April, 1915, in the usual manner. The cast was discarded during August, 1915, and he began to work in an ammunition factory. He has been seen once every three months since. He is absolutely free from pain, and there is very little restriction of motion in spite of the fact that his work is very laborious, consisting of carrying shells weighing up to 50 pounds. He has not lost a day during the year. This is the first time, in Finkelstein's knowledge, that the Albee operation has been done for spondylitis deformans, and in view of the results obtained, he believes it has a distinct indication in (1) those cases where the disease is localized, (2) in the early stages before the disease has progressed, (3) where there is an acute exacerbation in a chronic process, (4) where there is abdominal breathing which is interfered with by spinal brace or spinal cast, (5) as a last resort in those hopeless cases where all other methods have been tried and found wanting.

Felons.—DORRANCE (*Ann. Surg.*, 1916, lxiv, 716) says that he has 47 cases on file since his last paper on this subject, followed from beginning to end. Of these, 40 cases were opened within the first forty-eight hours, and complete cure ensued. Of the other 7, 5 were done after fifty hours had elapsed. Of the first two series the results were better than he has seen from longitudinal incisions, and of the last 2 cases, one had to have the phalanx removed while the other recovered only after a long and tedious treatment with a deformed finger. Dorrance makes an incision starting at the base of the nail on one side and extending in the line of the furrow over the tip of the finger, down on the other side to a point on a level with the beginning of the incision, in that way making a flap of the tip of the finger. It can be dogmatically stated that if the procedure is followed out properly, observing the rules, loss of sensation in the tip of the finger never occurs and the final result will be practically a normal finger. He concludes that all felons are caused by puncture wounds. Cases must be treated within forty-eight hours to get a perfect result. Cases over seventy-two hours' standing have usually damaged bone. Nitrous oxide is advisable in the majority of cases. The length of time required for perfect function depends upon the time elapsing before treatment is instituted. Restoration of function is quicker by this method than any other tried in Dorrance's experience.

THERAPEUTICS

UNDER THE CHARGE OF

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A Critical Study of One Hundred and Twenty Cases of Late Syphilis.—WILE and ELLIOTT (*Jour. Am. Med. Assn.*, 1916, lxvii, 1916) present this study with particular reference to the effect of early treatment upon the development of late manifestations of syphilis. A definite history of treatment with particular regard to time of inception and character was obtainable in all the cases studied. Fifty-five cases had absolutely no treatment whatever. In the remaining sixty-five treatment had been inefficient except in one single case. In other words, but one case of the entire group had had what would be deemed, under the accepted criteria of today, intensive treatment. To sum up these figures, almost 50 per cent. of the cases had received no treatment whatever, and of the remaining cases in which treatment had been administered, with the exception of a single case of precocious malignant syphilis, the treatment had been desultory and unintelligently carried out. Inasmuch as it was found that over 30 per cent. of the cases occurred before the end of the fourth year, it seems fair to compare this series with a number of other cases which had been observed over the same period of time and in which treatment had been instituted at the outset and carried through intensively. Of such cases they had forty which they have been able to follow for the four years following their infection. These patients have all received repeated injections of salvarsan followed by vigorous mercurialization in the form either of inunctions or injections. Of this number, 36, or 90 per cent., have reached the fourth year without any signs of recurrence, and the largest percentage of these cases are serologically cured. Of the 4 cases in which there has been recurrence, two patients have returned with central nervous system involvement in the nature of neural recurrences which yielded promptly to treatment. One patient had recurrent mucous patches, notwithstanding vigorous treatment, and the last was the precocious malignant syphilid mentioned before. By far overshadowing all other causes of the appearance of late syphilitic sequelæ, the lack of, or inefficiency of treatment during the early period stands out as the most important factor. The inefficiency of treatment by the ingestion of pills is suggested by the fact that in some cases in which treatment was given the largest number had been treated in this fashion. The tendency for late sequelæ to appear increases up to the fourth year, which represents a fastigium after which there is a decrease in the probability. That no latent untreated cases are immune is suggested by the lapse of forty-four years after infection in one of the cases. Trauma probably plays a smaller role in the production of active syphilis during the period of latency than is generally supposed. Where it occurs it is likely

to influence the appearance of gummatous lesions in or around the skeletal structures. Intensive treatment as accepted by modern methods (salvarsanization and thorough mercurialization during the early months) is protective in the largest percentage of cases. In treated cases the occurrence of late sequelæ, except for isolated and exceptional cases, must be regarded as an indictment against the method of treatment.

The Control of the Nausea and Vomiting of Pregnancy by Intramuscular Injections of Corpus Luteum Extract.—Hirst (*Jour. Am. Med. Assn.*, 1916, lxvii, 1848) presents the results of further experience with the use of corpus luteum extract as a therapeutic measure for the nausea and vomiting of pregnancy. Hirst has now treated 25 consecutive cases, without any attempt to choose the favorable or eliminate the unfavorable. Corpus luteum extract injected intramuscularly was successful in controlling the nausea and vomiting in 21 of the 25 cases, and in four it proved a complete failure. The smallest number of doses in any successful case was four. The largest number of doses was forty-two, but the nausea had ceased after the tenth dose in this case. The dosage depends upon the severity of the symptoms. The remedy as used by Hirst is in the form of ampules, each containing one-third grain of soluble corpus luteum powder in 1 c.c. of salt solution, saturated with chlorbutanol for its local anesthetic effect. This amount is equivalent to $2\frac{1}{2}$ grains of dessicated gland. The injections have not produced abscesses and there have been no untoward symptoms following its use. Hirst believes that the effect of corpus luteum as a factor in controlling the nausea of pregnancy has not received the attention it deserves and hopes that a more extended trial will sustain his belief in its efficacy as a therapeutic procedure.

The Incidence and Treatment of Entameba Histolytica Infection.—Dobell (*Brit. Med. Jour.*, 1916, 2914, 612) compares the results obtained by treating amebic dysentery by subcutaneous injections of emetic hydrochlorid with those obtained by the oral administration of emetin bismuth iodid. Emetin hydrochlorid was given by subcutaneous injection to a group of 21 cases of amebic dysentery. The dosage for each patient varied from eleven to fourteen daily injections of one grain each. The stools were frequently examined during the treatment and for considerable periods of time after the completion of the treatment. Of the 21 patients thus treated, 7 were apparently cured, 5 were not even temporarily freed of amebæ and the remainder all promptly relapsed. In those cases relapsing the amebæ were again found in the stools at intervals of from one to sixteen days after the treatment was discontinued. Eleven of the 14 cases that failed to respond to emetin hydrochlorid were then given emetin bismuth iodid by mouth in doses of one grain three times a day for periods of twelve days. Everyone of these patients was promptly and apparently permanently cured. There were no untoward symptoms that followed the use of the drug by mouth except nausea in a few instances. The 3 remaining cases that had previously relapsed after treatment by emetin hydrochlorid were treated by a second course of the same preparation in daily doses of one

grain. Two of these were not even temporarily benefited by the treatment, while the third was freed of the amebæ for only three days and the infection then recurred. Two of these same 3 patients were then given emetin bismuth iodid and both were completely cured. Dobell then tried the effect of the remedy on a series of ameba carriers and a prompt cure was obtained in all. He believes that it is the most efficient remedy for carriers—affecting the encysted form of the parasite more certainly than does emetin hydrochlorid. It is interesting to note that many of the patients were infected with other parasites: Entameba coli, lamblia and chilomastix, and in no case were these parasites removed from the feces by any form of emetin treatment. The entameba coli disappeared during treatment in some instances, but promptly recurred after the discontinuance of the treatment.

The Quantitative Effect of Salvarsan on the Wassermann Reaction of the Blood.—King (*Jour. Am. Med. Assn.*, 1916, lxvii, 1669) says that in most cases little change occurs in the strength of the Wassermann reaction during the first five days following the administration of salvarsan. In a series of twenty treatments, only 1 case, in the primary stage, showed a marked weakening of the test. Some previously untreated cases may be given prolonged salvarsan therapy with very little weakening of the Wassermann reaction. Such cases may, however, show striking improvement symptomatically. In this series only one insignificant temporary increase (provocative reaction) in the complement-binding substance could be demonstrated, following the administration of salvarsan, The author thinks it is improbable that over short periods of time, there occurs any marked spontaneous fluctuation in the amount of complement-fixing substance in the blood of syphilitics, Definite proof of the existence of the provocative Wassermann reaction following salvarsan is not at hand at the present time.

A Further Report on Thromboplastin Solution as a Hemostatic.—Hess (*Jour. Am. Med. Assn.*, 1916, lxvii, 1717) has found that tissue juice made from brain (thromboplastin solution) has proved itself of practical value in controlling hemorrhage wherever it can reach the site of bleeding. In cases of true hemophilia it may be regarded almost as a specific hemostatic. It is to be recommended for local use in the bleeding of the newborn, in nasal hemorrhage, and in the parenchymatous bleeding associated with various operations. Where local applications fail, it should be injected into the site of hemorrhage, as in bleeding from the gums following tooth extraction. This method can readily be resorted to, as thromboplastin solution loses but little of its potency as the result of dilution and cursory boiling. Further clinical experience is necessary before its value can be determined as a hemostatic in connection with hemorrhage of the gastro-intestinal tract. However, it is innocuous when given by mouth in considerable dosage, and would seem to be indicated in bleeding from the stomach and from the upper intestine. Hess says that, in addition to its hemostatic action, this tissue extract has been found to possess healing properties, actively stimulating granulation tissue and hastening epithelization. It is therefore applicable as a dressing for torpid ulcers and sluggish wounds.

PEDIATRICS

UNDER THE CHARGE OF

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The Neuropathic or Nervous Child.—E. B. AUGELL (*New York State Jour. Med.*, 1917, xvii, 13) in a discussion of the nervous child quotes Dr. Francis Warner's description of the typical signs of the nervous child. Nervous children are apt to complain of headaches, are poor sleepers and hard to put to sleep, talk in their sleep and grind their teeth, and are tired on arising. They are delicate without having any disease and are rarely attacked by illness. They are not strong, cannot walk far without tiring; some days they are too tired to do anything and must rest. Their appetite is capricious and they easily loose weight. They are generally well made in body, but may be tall and rather thin, with subnormal body weight. In nerve signs they give evidence of weakness and overspontaneity. Augell lays emphasis on the study of the physiognomy and muscle action in the observation of children and suggests a well tried out test employed by Dr. Warner. In asking a child to extend its arms in imitation of your own example, the arms should come out parallel, hands almost on a level, fingers when extended are curved slightly downward from the wrist with the thumbs closely applied to the hands, a position which denotes the balanced action of a normally acting brain. The nervous child, however, shows a different result. If tired, there is drooping of one arm below the other, the thumb drops away from the hand and in extreme cases the hands drop from the wrist. If the nervous system is in a tense, unbalanced condition the fingers are overextended with the knuckles inclined slightly backward marking overmuscular action. This sign was noted in 25 per cent. of the author's cases. Augell is inclined to regard nervousness in children as dependent on ill-balanced nervous control rather than exhausted nervous energy. The relation between muscular and brain activity is very direct and Augell impresses the value of trained muscular exercise in increasing the size of the motor convolutions of the brain as well as the depth of the cortex and in developing ready control and quick response in the mind. He cites military drill as exceptionally valuable in this respect and in developing self-control which is a vital factor in the treatment of the nervous child. Neurotic inheritance plays a more important part in childhood neurosis than in the adult type. In 80 cases of typically nervous children, 70 per cent. gave a history of neurotic inheritance. The arthritic diathesis is another important factor, about 30 per cent. giving a family history of arthritic trouble in the immediate ancestry. Among a list of physical conditions and abnormalities which cause nervousness Augell mentions bad oral hygiene, disorders of the digestive tract or faulty metabolism, especially a too high protein diet, and conditions due to bad ventilation in home and school.

Little's Disease.—JOSEPH S. WALL (*Arch. Pediat.*, 1916, xxxiii, 812) brings out the various conceptions held by different authorities on this malady, showing quite a diversion of opinion as to what class of cases of spastic paraplegia should be designated Little's disease. Spastic paralysis, because seen in infancy and childhood should not be classed as Little's disease solely for that reason. Wall states that Little's disease appears to represent cases of congenital spastic rigidity or paralysis having their origin before or during the act of birth from causes within the central nervous system, particularly the cerebrum and that this excluded the whole group of spastic paraplegias occurring during infancy as well as those paralyses dependent upon peripheral lesions. The causative factors are both prenatal and natal. Prematurity apparently is held to be the main general factor, whether the effects are due to undeveloped fibers in the pyramidal tracts of the brain or as the French writers believe, to syphilis either in the father or mother. However, prematurity in itself may be questioned as originating Little's disease since so many premature infants grow and develop into healthy beings. Next to prematurity, perhaps intimately associated with it among prenatal factors, should be placed syphilis. The French school has brought many arguments to prove that syphilis is the most common cause of the disease. Natal causes include hemorrhages from trauma during labor. Basal hemorrhages are usually fatal while those of the cortex permit of life and the consequent degenerations shown in Little's disease. Asphyxia neonatorum has been noted in from one-third to one-half of many of the recorded cases. It would seem difficult, however, to differentiate between asphyxia as a cause of hemorrhage and asphyxia as a result and symptom of hemorrhage which has preceded the state of suspended animation. The pathological changes causing the paralyses and spasticities taken collectively show hemorrhage, meningeal and cortical, defect degeneration and inflammation. Primary destruction or non-development of the brain surface is largely responsible for the production of the syndrome of Little. Early symptomatology includes spasticity of the extremities and trunk, inability to support the head or retraction of the head, incoördination of the upper extremities, asymmetry of the face, difficulty in attracting the attention of the eyes, strabismus, "choking sounds" and laryngeal stridor. Later on lack of proper development and infantile growth become apparent and the symptom-complex depended upon the degree of cortical involvement.

OBSTETRICS

UNDER THE CHARGE OF

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Cases of Apparent Appendicitis Complicating Pregnancy.—VAN TRIM (*Ann. de gynéc. et d'obst.*, 1916, xlii, 177) draws attention to the occurrence of symptoms in pregnant women precisely simulating those of

acute appendicitis. In the first a gangrenous diverticulum was found at operation while the appendix was normal In two other cases the symptoms were caused by suppurating dermoid ovarian cysts. The fourth patient had classic signs of sudden pain in the right lower abdomen, but at operation the cecum and appendix were healthy. A collection of blood was found extending into the iliac fossa behind and below the uterus and broad ligament. The case proved to be one of intra-uterine pregnancy and also ruptured tubal pregnancy. The fifth case was postpartum, and the symptoms were caused by the twisted pedicle with partially suppurating ovarian cyst. It is not uncommon in parturient and puerperal women to have bilateral pain described in the lower abdomen. Occasionally this pain is unilateral and can often be traced directly to the region of the ovary. In some patients this pain follows nervous or psychic shock and is attended by no physical symptoms. In making a differential diagnosis the obstetrician should remember that young women may have an acute infective process with normal temperature and without rigidity of the abdomen, the cardinal symptom being high leukocytosis and the complaint of pain. This pain may occur periodically, and may strongly simulate the pain of hysteria. Great help is obtained in diagnosis by the examination of the blood to determine the degree of leukocytosis present and the bacterial examination of the urine to determine the presence or absence of colon bacillus infection of the kidney. Two cases in the experience of the reviewer illustrate this point. In the first, a young woman with a normal temperature was suffering from infection following a criminal abortion. She had no rigidity of the abdominal muscles and slightly subnormal temperature and rapid pulse. There was a foul discharge from the uterus. On admission to the hospital her condition was so grave that operation could not be performed. At autopsy rupture of the pyosalpinx and acute infection of the peritoneum were present. In a second case a young woman had produced upon herself abortion by inserting a slippery elm stick. She had a normal temperature, not much abdominal rigidity, but complained periodically of severe abdominal pain. Her leukocytes were above 21,000. The pain was so pronounced and came so regularly that it seemed hysterical in character. On section both Fallopian tubes exuded pus, the general peritoneum was injected, and the appendix was normal. This patient did well with drainage of the pelvic cavity.

Migrating Phlebetis.—Hedblom (*Jour. Am. Med. Assn.*, 1916, lxvi, 1777) reports the case of a woman, aged twenty-eight years, in her fourth pregnancy occurring during five years. The first two children had died of exhaustion, the third was living and well. At the end of twelve hours a fairly developed child was spontaneously born. There was no laceration and the placenta came away spontaneously. The uterus did not contract well and there was more than the usual loss of blood. On the eleventh day of the puerperal period the patient had severe night sweats followed by fever. The white blood corpuscles were 17,000, hemaglobin 60 per cent. There was inflammation of the right saphenous vein which gradually subsided. This was followed by inflammation of the other veins in the left side of the neck, axilla, arm and chest. This subsided to be succeeded by swelling in the other portions of the

body. In all the patient had six relapses, each attended by more or less severe constitutional prostration. The patient finally recovered and was discharged in the nineteenth week in good general condition.

The Combination of Morphin and Pituitrin in Labor.—Olivella and Arteaga (*Rev. méd. de Sevilla*, 1916, lxvi, 199) in 7 cases reported good results by using a combination of the hydrochlorate of morphin and extract of the fresh pituitary body and a sterile vehicle. Pain was greatly diminished, uterine contractions were better and the general condition of the patient remained good. Postpartum vomiting occurred in one case only and involution was normal. One child was born apneic, but was readily revived. The children seemed stupid and breathed languidly during the first twenty-four hours after birth, and required special care.

Joined Twins.—Iyer (*Indianapolis Med. Gaz.*, 1916, li, 237) reports the case of a woman who had been in labor three days. On examination a fetal head and left forearm had been delivered. A second head with its face turned toward the delivered one was also found. This could not be pushed up, so it was delivered with forceps without much difficulty. Both children were removed through the uterus and a common placenta was expressed shortly afterward. On examination it was found that the twins were attached by the cartilage of the ribs. There was a common abdomen covered only by peritoneum, but there were separate pelvic bones and pelvic organs. There was one cord and one liver and spleen. There were two pairs of kidneys, a single heart, one diaphragm, and two lungs.

Morphin-hyoscin Method of Painless Childbirth.—Haultain (*Brit. Med. Jour.*, October 14, 1916) states that the method of Krönig and Gauss had not been accurately followed by the majority of the British obstetricians who have used the drugs. In the Royal Maternity Hospital in Edinburgh, Haultain and his staff rigidly adhered to Krönig's technic in the first 8 cases and the results were satisfactory. He observed that patients sometimes became restless and highly excitable and this seemed to be a personal peculiarity of the individual case. With some patients more than twenty-two injections were given during labor. Where it was impossible to obtain separate rooms for the isolation of the patient, the ward was darkened and screens placed about the patient's bed and cotton placed in the ears. Forty cases were so treated, 36 primiparæ, and 4 multiparæ. The smallest number of injections was 4 and the greatest 45. Usually $\frac{1}{4}$ grain morphin was given at the beginning with $\frac{1}{150}$ hyoscin. In 3 cases $\frac{1}{6}$ grain morphin was first used. In 3 cases morphin was repeated and the second dose was $\frac{1}{8}$ grain. In 30 out of 40 amnesia and analgesia were obtained. There was some effect in every case. In 3 cases the method failed. In 1 case there was marked restlessness and injections had to be stopped. Postpartum hemorrhage occurred in one case and in 14 patients the forceps had to be applied. In 5 of these the instrument was used without chloroform and in the others chloroform was given. Of the 40 children, 5 were dead born, and of the 35 born living, 4 required artificial stimulation. In using the method in a primipara

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the first injection must not be given too early, as it tends to stop the pains. When the os admits two fingers and pains are regular the drugs may be employed. In a multipara the injections can be begun as soon as labor starts. The second injection, $\frac{1}{150}$ grain hyoscin should be given about one hour after the first injection, and this can be repeated at intervals of one hour or three-quarter of an hour afterward. The morphin should not be repeated in the latter part of the second stage, because it tends to produce asphyxia in the child. The advice is given that if the hyoscin is not taking effect it is well to give the mother a slight whiff of chloroform. Thus the hyoscin is allowed to work and the patient passes into the condition of "twilight sleep." Thirty-seven of the 40 patients got up out of bed on the third day after labor. We are somewhat interested to observe that the writer describes the administration of morphin-hyoscin as the method of Krönig and Gauss. They employed scopolamin, and laid great stress upon the absolute purity and quality of this drug. There is nothing new in the employment of hyoscin with nervous patients whether they be pregnant or not, and morphin has long been known to be useful with nervous patients during labor. The suggestion to give chloroform to permit the hyoscin to take effect is an extraordinary method of treatment, and one which does not appeal to us. We do not observe that the results of this treatment were especially satisfactory in avoiding the use of forceps, and yet it is supposed that if the patient be spared suffering her strength will be conserved and the use of forceps will be reduced to a minimum. After being extensively exploited by the public press, and after a determined effort had been made to make the scopolamin method popular with the public, it has passed into the category of medical nostrums of doubtful value. The only benefit to the public and the profession which its attempted introduction produced was the study of the best and safest methods of lessening pain during labor, and this brought out clearly that the scopolamin-morphin method was difficult of application, uncertain in results, frequently producing asphyxia in the child, lengthening labor, and much inferior to other reliable and safe methods of treatment.

The Midwife Problem in England. — In the *Brit. Med. Jour.*, September 16, 1916, occurs the annual public health report of the city of London. This shows that the expectation of life for men and women is lengthened, especially in the case of women for all periods of life. The birth-rate diminishes steadily and is now 24.3 per thousand. The death rate 14.4 per thousand. The infant mortality rate is also lessening; 104 per thousand. Midwives are licensed and under control, but the compensation which they receive is so small that very few of them can rely solely on their practice as a means of livelihood. Some increase their incomes by keeping lying-in homes and others give instruction to pupils. It is estimated that 25 per cent. of the total births of London are attended by midwives. There is, however, a general tendency on the part of the midwives to call medical help more frequently. There is still considerable mortality from puerperal septic infection, 393 cases being reported, 113 of which proved fatal.

GYNECOLOGY

UNDER THE CHARGE OF

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Fatal Results of the Percy Treatment.—The method of treating inoperable uterine carcinoma by means of the so-called "cold iron" cauterization, advocated by Percy, has aroused much interest in this country in the past two or three years, and has been previously discussed in this department. So far, it has been practically impossible to get any definite statement of results from Dr. Percy himself, although he has been extremely enthusiastic regarding the possibilities of his technic, and a number of other surgeons have reported more or less favorable immediate results. As yet the method is too new to admit of judgment as to its ultimate accomplishment. That the immediate effects of this method of treatment may not be as devoid of danger as has been claimed is well shown, however, by a recent report from LEONARD and DAYTON, (*Surg., Gyn. and Obst.*, 1917, xxiv, 156) recording two postoperative deaths. The first patient was fifty-two years of age, and entered the hospital with an inoperable carcinoma of the cervix, with masses in each broad ligament. The uterus was cauterized for an hour by the Percy method, and then the point was introduced for a half hour into each broad ligament mass. In this, as in the other case reported, the full Percy technic (abdominal control of heat, ligation of internal iliacs, etc.) was carefully carried out. The patient developed symptoms of ileus, and died suddenly on the fourth day. At autopsy about 24 round ulcers were found in the stomach; there was a vesicovaginal fistula, and the tissues surrounding the cervix were destroyed, having a foul odor, and necrotic, putty-like consistency. Beyond this necrotic mass, however, perfectly preserved carcinoma was found. The immediate cause of death was a pulmonary embolus. The intestines were greatly distended, but no anatomical obstruction could be found. There were also pulmonary edema, hemorrhagic serous effusions, extreme cloudy swelling of the viscera, and renal epithelial necrosis—lesions which with the gastric ulcers presented a picture very similar to that seen after extensive superficial burns. It seemed possible, therefore, that death in this case may have been due, in part at least, to the same unknown factors. The second patient was about the same age, but entered the hospital with a very early carcinoma on one lip of the cervix. A typical Wertheim operation was done, but within six months she returned with a recurrence in the left broad ligament, which contained a firm, fixed mass about 5 cm. in diameter. This was treated by the insertion of the Percy cautery tip into the center of the mass, thoroughly heating it for two hours. The patient's condition was excellent for four days, when incontinence of urine developed and the temperature went up to 105°, eventually reaching 108°. Blood cultures showed streptococcci, and on the sixteenth day the patient died. At autopsy a vesicovaginal fistula was found in this case, also, with a soft, gray necrotic mass of tissue extending out into the left broad ligament. At one point in the broad

ligament, just beyond the zone of coagulation, living carcinoma tissue was found. The cause of death in this instance was the streptococcus septicemia. From these two cases, the authors draw the conclusion that not only does the Percy method fail to kill off completely the cancer cells, but that it leaves a sloughing, coagulated mass of tissue which offers an ideal medium for the growth of microörganisms. It probably will be found impossible always to prevent infection of this area, and once infected the thrombosed vessels of the region offer a ready entrance into the system.

Syphilis of the Bladder.—Baker (*Surg., Gyn. and Obst.*, 1917, xxiv, 187) draws attention to the fact that while until quite recently this lesion was considered extremely rare, its very existence being denied by some authors, our increasing knowledge of urology has shown that syphilis will have to be given a more prominent place in the etiology of urinary disturbances. A sufficient number of authentic cases of bladder syphilis are on record to leave no doubt as to its existence, though no definite symptomatology has been established. It has been well said that syphilis is the great imitator, producing symptoms and lesions closely resembling those of many other diseases, and this is true of its vesical manifestations. The most common symptom is increased frequency of micturition, one of the most striking features being usually the extreme sensitiveness of the bladder, this being the more marked the closer the lesion, especially an ulcer, is to the vesical orifice. Urgency is always extremely marked, the symptoms thus resembling somewhat renal and vesical tuberculosis. The urine may show nothing but a few red blood cells, or may be frankly hemorrhagic; pus is usually absent, as are bacteria, and spirochete have never been found. The type of lesion found on cystoscopic examination varies according to the stage of the disease. In the secondary stage there may be small macules, or small multiple superficial ulcerations, with hyperemic mucosa. In the tertiary stage the lesions are of two types; the gummatous ulcer and the papillomatous tumor, both of which may exist together. These ulcers are usually single, with ragged indurated margins, grayish bases, and a surrounding zone of deep red color. The papillomatous tumors may resemble either carcinoma or the ordinary benign tumor; their surfaces are frequently ulcerated, and may be covered with incrustations. The most common site for both secondary and tertiary lesions is the base of the bladder, just external to the ureteral orifices but they may be found on any part of the wall. It is common to find the vesical orifice in females greatly swollen and irregular, or to find a gummatous tumor in this region. The tertiary lesions show no tendency to spontaneous cicatrization, but tend to progress to the point of perforation. The absence of ulcers, vegetations, etc., should not rule against the diagnosis of syphilis, however. Excessive swelling and hyperemia of the vesical mucosa, either diffuse or patchy, associated with the symptoms of a cystitis unresponsive to local treatment, the absence of all common etiological factors, and especially the absence of infection in the urine, with a positive Wassermann, and the prompt disappearance of all symptoms and lesions after antisyphilitic treatment should constitute, in the author's opinion, sufficient evidence for the diagnosis of syphilis of the bladder.

HYGIENE AND PUBLIC HEALTH

UNDER THE CHARGE OF

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PROFESSOR OF PREVENTIVE MEDICINE AND HYGIENE, HARVARD MEDICAL SCHOOL, BOSTON, MASSACHUSETTS,

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JOHN F. ANDERSON, M.D.,

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Typhus Fever.—S. B. GRUBBS (*United States Public Health Reports*, 1916, xxxi, 42, 2918) describes new methods adopted at the Boston Quarantine for destroying lice on typhus fever suspects. After undressing, the suspect is sprayed from head to foot with a gasoline soap solution. This is soap one, water four, gasoline four parts, to make the stock which is diluted with five to ten parts of water before using. After being sprayed he goes into a large shower bath and can be relied upon to wash the soap off thus saving the supervision usually necessary for unwilling bathers. Clothing is treated in a disinfecting chamber by a vacuum-cyanide method. The article enumerates some of the experiments that have been made. These demonstrate that lice can be killed not only in bundles of clothes but also in tightly packed and closed trunks. For this purpose a 20 inch vacuum is created in the disinfecting chamber, hydrocyanic acid gas from four ounces of sodium cyanide per one hundred cubic feet of chamber capacity is then introduced and left in for thirty minutes. The time may possibly be shortened by improved apparatus but as the handling of the clothing or baggage by the station force is unnecessary the greatest loss of time and trouble is eliminated and the owner has his possessions returned to him exactly as they were surrendered. This method presents the great advantage of not requiring baggage to be opened or even unlocked. As every piece must be unpacked and the contents sorted if steam or dry heat is used and besides this must be dried if immersed in insecticide solutions the advantage in handling large quantities of baggage is striking. As the process is entirely safe its application need not be limited to typhus fever suspects but may be used in lodging houses and similar institutions where it is necessary on account of vermin, to regularly disinfect the bedding and clothing of the inmates.

The Milking Machine a Source of Bacterial Contamination of Milk.—RUEDIGER (*Jour. Infect. Dis.*, October, 1916, No. 4.) made a study of the milk delivered to retailers in La Salle and Peru, Illinois, and found that milk which had been drawn by a milking machine almost invariably gave higher bacterial counts than those which had been drawn by hand. An investigation was made and milk drawn by hand from a cow into a sterile bottle. The milking machine was then used in the condition in which it was ordinarily kept, and also after the cups, tubes and cans had been sterilized by drawing a pailful of boiling hot water through them. The figures collected from this

investigation show that milk may be grossly contaminated by using an unclean and unsterilized milking machine. The water used for scalding should be boiling in order to be effective and immersion in a solution of "B. K." or chlorinated lime does not satisfactorily prevent the growth of bacteria.

Comparison of a Rapid Method of Counting Bacteria in Milk with the Standard Plate Method.—FROST (*Jour. Infect. Dis.*, September, 1916, No. 3) describes a rapid method of counting bacteria in milk. A comparatively low dilution of milk is made with nutrient agar, spread over a definite area on a microscopic glass slide and incubated only until the small colonies are visible under a compound microscope. The culture is then dried and fixed in the flame and stained with methylene blue, which is partially washed out, leaving the colonies a deep blue while the agar background is only tinged or quite clear. The counting is done under the low power of the compound microscope. Thirty-seven samples of milk, which varied in content from 675 to 20,000,000 bacteria per cubic centimeter, were compared. Each of these samples was analyzed by the standard method and by the rapid method, and the results obtained showed satisfactory correspondence between the two. With the exception of two samples all were placed in the same class by both methods. If the result obtained by the standard is taken as 1, the result with the rapid method was 1.6 for class A, milk with a bacterial count of from 0 to 10,000; 0.89 for class B, with a bacterial count of from 10,000 to 100,000; 1.9 for class C, bacterial count 100,000 to 1,000,000; 0.62 for class D, bacterial count 1,000,000 to 10,000,000. The number of bacteria obtained per cubic centimeter of milk varies with the magnification used in counting the colonies. Greater variations existed with the little plates than with the standard plates, because, under the higher power, groups of bacteria dead or not yet grown into colonies were counted. The necessary period of incubation for the little plates varies from three to twelve hours. With the little plates a much larger amount of milk is used than with the standard plates, hence the former method ought theoretically to be the more accurate of the two. The rapid method permits the examination of young colonies of bacteria and the recognition of individual microörganisms which is not possible by the standard method.

Comparison of the Rate of Multiplication of Bacteria in Raw Milk with the Rate in Pasteurized Milk.—ALLEN (*Jour. Infect. Dis.*, 1916, xix, 721) found that raw milk as compared with pasteurized milk exerts a powerful suppressing influence on the multiplication of certain bacteria. When Bacillus lactici-acidi is accustomed to the milk of a certain cow, apparently no killing of this organism takes place in freshly drawn milk. When a single cell of certain pronouncedly chromogenic kinds of bacteria is added to fresh milk, the organism is found plentifully in the milk after sixteen hours at 20° C., the injurious action of freshly drawn milk not being sufficiently intense to kill the one bacterial cell. After pasteurization the organisms which remain in the milk and those which are able to get into the milk find conditions more favorable for their rapid multiplication than before pasteurization.

PATHOLOGY AND BACTERIOLOGY

UNDER THE CHARGE OF

JOHN McCRAE, M.D., M.R.C.P.,

LECTURER ON PATHOLOGY AND CLINICAL MEDICINE, MC GILL UNIVERSITY, MONTREAL; SOME TIME PROFESSOR OF PATHOLOGY IN THE UNIVERSITY OF VERMONT, BURLINGTON, VERMONT; SENIOR ASSISTANT PHYSICIAN, ROYAL VICTORIA HOSPITAL, MONTREAL,

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PROFESSOR OF PATHOLOGY AND BACTERIOLOGY, UNIVERSITY OF PITTSBURGH, PITTSBURGH, PA.

Streptothrix in Bronchopneumonia in Rats Similar to That in Rat-bite Fever.—Through the work of Blake attention has been called to a type of streptothrix which is probably the infecting organism in rat-bite fever. Since this report there have been too few cases to finally establish the common nature of the infection for all. The question of the origin of the streptothrix in the rat still remains unsolved. TUNNICLIFFE (*Jour. Infect. Dis.*, 1916, xix, 767) brings forward evidence to indicate that the rat is a carrier of this infection and is subject to bronchopneumonia from this source. Chronic bronchopneumonia was encountered in 60 white rats and in 56 of these a filamentous organism was observed in smear preparations. Cultures of a streptothrix were gained from 20 of these animals. This streptothrix was pathogenic in a number of normal animals inoculated. The microörganism corresponds morphologically and culturally with the Streptothrix muris-ratti as described by Blake. The infected animal showed an increase in opsonins and agglutins for this microörganism.

Experimental Arteriosclerosis of the Aorta and the Coronary Arteries of the Heart.—KRYLOV (*Compt. rendus de la Soc. biol.*, 1916, lxxix, 397) experimented on rabbits with the object of verifying the work of several previous writers, who maintained that the feeding of cholesterin or of food rich in cholesterin to rabbits produced in them characteristic changes similar to those observed in atheroma in man. The author fed his rabbits yolks of eggs, varying from 182 to 198 grams in quantity, and cholesterin, varying from 40 to 50 grams; then let them rest two weeks to six months. During the period of rest, fats and lipoid substances, particularly the doubly refracting ones, accumulated in the deep portion of the intima which was divided into two parts; a compact layer poor in cells but rich in collaginous and elastic fibers with few muscular elements and no fat, and below this a varying but always considerable quantity of fats and lipoids. These substances in the liver, spleen, and bone marrow are absorbed during the period of rest; in the aorta, however, conditions exist which are particularly unfavorable to their reabsorption, a fact which plays an important part in the development of arteriosclerosis. The predominating cellular

elements of the layer rich in fats are phagocytes of cholesterin, which undergo fatty degeneration and final calcification. The author further established the fact that, as in human atheroma, the process extended from the aorta to the smaller arteries, especially the coronaries. Limited to certain parts of the wall in the large arteries, it often spread over the whole surface of the small arteries and extended even to their finest ramifications. It began in a thickening of the intima by a deposit of fat and doubly refracting lipoids under the endothelium and with increased deposit led to the narrowing of the lumen. In the thickened intima variable quantities of cellular and muscular elements appeared in the process of degeneration. A period of rest after feeding had the effect of increasing the cellular elements in the tissues infiltrated by fat. The elastic tissue played a large part in the encroachment of the areas and the thickened intima of the vascular wall became a permanent characteristic.

A Note on Experimental Nephropathy.—STODDARD and WOODS (*Jour. Med. Res.*, 1916, xxxiv, 343). The endotoxins of streptococci isolated from meningitis, or staphylococci from osteomyelitis, and the poisons of Vaughan's split products of the tubercle bacillus were daily injected intravenously or subcutaneously into rabbits for twenty to twenty-six days. The rabbits were then killed and autopsied immediately. The kidney lesions consisted essentially in an epithelial degeneration of the first division of the proximal convoluted tubules, with thickening and edema of the protoplasm and loss of the cellular membrane between adjacent cells, a diffuse process bordering on protoplasmic disintegration leading to a finely granular débris in the lumen of the tubule. The cells of the ascending loop of Henle contained a granular yellowish brown pigment. The distal portion of the convoluted tubules remained normal. These lesions were observed following the action of the poisons of the tubercle bacillus. The staphylococcic and streptococcic endotoxins, prepared according to the technic of Macfayden, produced different lesions from those just described and consisted in vacular degeneration with transformation of the epithelial cells into a tubule resembling fat tissue. This process was seen especially in the proximal and middle portions of the proximal convoluted tubule. There were no membranous lesions; the glomeruli appeared normal except for occasional slight thickening of the capsular and capillary walls. These changes differed according to the duration of the intoxication; the treatment with tuberculous products lasted twenty days. Rabbits received several inoculations of cocci heated to 56°, and killed in physiological salt solution. The authors call attention to the fact, however, that the lesions produced by proteins extracted by Vaughan's method, differed from those reported by Longcope and Boughton.

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In a paper on Corpus Luteum in the January 29th number of the New York Medical Journal, Dr. Sajous states:

> "The two most important prerequisites to success in the use of the drug appear to be:
>
> "1. The selection of a preparation made exclusively from the corpora lutea of pregnant animals, and
>
> "2. Due attention to the fact that the action of the drug is frequently slow in asserting itself and that the drug should be given up only when thorough trial has demonstrated its lack of efficiency."

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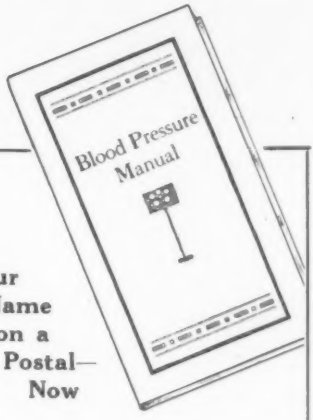

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